The Association Between Immunization Information Systems and Immunizations in Children 19-35 Months of Age in the United States.

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Abstract

In 2017, only 70.4% of U.S. children ages 19-35 months were up-to-date (UTD) for their routine series of vaccines, a rate that consistently misses the national target of 80%. Recent evidence has demonstrated that those rates are declining. As a result of an under-vaccinated population, vaccine preventable disease outbreaks are becoming more frequent and places vulnerable populations at risk for disease, disability, or death. Contributors to sub-optimal immunization rates include challenges in identifying vaccination needs, incomplete or inaccurate vaccination records, missed opportunities, and vaccine hesitancy among parents and providers. One strategy to improve immunizations in the U.S. is through the utilization of immunization information systems (IISs). Although large investments into their infrastructure, implementation, and operation have led to widespread adoption of IISs by state immunization programs, research evaluating the impacts of these systems on immunizations is still in early stages and has resulted in mixed findings. The purpose of this dissertation is to explore the relationship of IISs on immunizations.

Using data from the National Immunization Survey, The IIS Legislative Survey, and the IIS Annual Reports (IISARs), I analyze the association of IIS policies and participation on immunization status in children 19-35 months of age. Following a three-essay format, I utilize a series of multiple logistic and linear regression models to examine the relationship between IIS participation on UTD status and invalid doses, and IIS policies and provider participation on state-level immunization rates. Consistent with the previous literature, my overall findings on IIS participation resulted in mixed findings. While there was little to no association between IIS participation and the odds of a child completing their full vaccines series, I did find a statistically significant relationship between IIS participation and the odds of invalid doses. Further, previous

studies found no association between mandate or consent policies on state-level UTD immunization rates. While supporting previous work, I also find a statistically significant interaction between mandate and consent policies as it relates to UTD rates. This work contributes to the literature by expanding what is known about how IIS policies and participation relate to immunization rates. These studies further highlight the dynamic but important relationships between policy, and participation by providers and parents that can inform future immunization improvement strategies.

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standing beside me through it all. Thank you to my parents, for teaching me how to be resilient and resourceful (and stubborn). Finally, to my amazing husband Sriharsha- words cannot express my love and gratitude. Day after day, you nudged me, supported me, and encouraged me to pursue every opportunity. You are my partner and my hero, and I cannot wait to see where we go from here!

Dedication

I dedicate this dissertation to the many influential people in my life who are not able to be with me today and especially to my mother. Mom, you taught me compassion, empathy and resilience; I hope I made you proud. I carry your love with me always and miss you with each passing day.

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List of Frequently Used Terms, Acronyms, and Abbreviations

Term	Definition
ACIP	Advisory Committee on Immunization Practices
CDC	Centers for Disease Control and Prevention
DTaP	Diphtheria Tetanus acellular Pertussis- current children's formulation
Full Series	4:3:1:3:3:1:4 series of vaccines (4 DTaP, 3 Pol, 1 MMR, 3 HepB, 3 Hib, 1 Var, 4 PCV)
HepB	Hepatitis B vaccine
Hib	H*aemophilus influenzae* type b vaccine
IIS	Immunization Information System
IISAR	Immunization Information System Annual Report
Pol	Polio vaccine- current U.S. vaccine- inactivated injectable
MMR	Measles, Mumps, and Rubella vaccine
MMWR	Morbidity and Mortality Weekly Report
NCIRD	National Center for Immunization and Respiratory Diseases
NIS	National Immunization Survey
IISAR	Immunization Information System Annual Report
IIS Leg	Survey of Immunization Information System Legislation
PCV	Pneumococcal vaccine
UTD	Up-to-Date for the Full Series
Var	Varicella zoster vaccine
VFC	Vaccines For Children
VPD	Vaccine-preventable disease

Chapter 1 Introduction

Background

In the United States (U.S.), vaccines prevented an estimated 322 million illnesses, 21 million hospitalizations and 732,000 deaths from 1994-2013 (Centers for Disease Control and Prevention, 2014; Whitney, Zhou, Singleton, & Schuchat, 2014). Since the uptake of widespread vaccination, along with improvements in hygiene, sanitation, clean water, and antibiotics discovery, morbidity and mortality of vaccine preventable diseases (VPDs) has been reduced by more than 99% for most diseases (Centers for Disease Control and Prevention, 1999; Roush & Murphy, 2007). They are widely cited as one of the greatest public health achievements and cost-effective preventive health measures of the 20th century saving the U.S. an estimated $295B in direct and $1.38T in society costs over the same twenty-year period (Control & Prevention, 2011; Whitney et al., 2014). In order to maintain the current disease reduction and gain ground on further reducing the incidence and burden of disease, high levels of vaccination need to be sustained (Andre et al., 2008b).

U.S. immunization policies focus primarily on childhood vaccines. Younger children are more at risk for contracting and spreading infections and for complications that can cause significant disability or death (Andre et al., 2008a). For most vaccines, rates of childhood vaccination have been relatively high (Hill, Elam-Evans, Yankey, Singleton, & Kolasa, 2015), but recent evidence over the last three years suggests that those rates are declining (Hill, Elam-Evans, Yankey, Singleton, & Kang, 2017) and consistently miss national immunization targets (Healthy People 2020 [Internet], Office of Disease Prevention and Health Promotion). Sub-optimal rates leave un-vaccinated or under-vaccinated individuals susceptible to vaccine-preventable diseases and have spurred increases in the frequency and sizes of outbreaks in communities (Constable, Blank, & Caplan, 2014; Malone & Hinman, 2003).

The contributors to lower immunization rates are well-established in the public health literature. Increases in the number of vaccines needed and the changes to the immunization schedule create difficulties in tracking immunization status by parents and providers (Butte, Shaw, & Bernstein, 2001). Tracking is further complicated by record fragmentation and scattering (Stokley, Rodewald, & Maes, 2001; Yusuf et al., 2002) which can result when a child has multiple providers or moves out of state since the U.S. lacks a universal electronic health record (Feikema, Klevens, Washington, & Barker, 2000; Orenstein, Douglas, Rodewald, & Hinman, 2005). Oftentimes, providers do not have access to a child's full vaccination history which prevents determining vaccination needs while at the point of care (Gostin & Lazzarini, 1995). Aside from electronic data factors, other reasons for low vaccination rates include increasing vaccine hesitancy by providers and parents which has increased the utilization of alternative, and unvalidated, vaccine schedules (Feemster & Offit, 2013; Offit & Moser, 2009).

The failure of the U.S. to increase immunization coverage motivated large investments into Immunization Information Systems as a strategy to improve rates (Hinman, Urquhart, & Strikas, 2007). IISs are confidential, centralized, electronic repositories that house vaccination data and offer many features designed to improve the overall quality and delivery of vaccines. IISs were designed to assist providers, hospitals, public health officials, and other stakeholders such as Medicaid plans (Freeman & DeFriese, 2003). They offer clinical decision support tools to assist providers in providing the age-appropriate vaccines using embedded algorithms based on the Advisory Committee on Immunization Practices (ACIP) recommended schedule and the patient's IIS vaccination history (Rajamani, Bieringer, & Muscoplat, 2015). IISs also help providers improve immunizations and quality through its Assessment, Feedback, Incentives, and eXchange (AFIX) program (American Immunization Registry Association, 2015). IISs can

provide immunization histories directly to patients or parents that can be useful for care coordination or for proof of vaccines for school entry (Galemore, 2011). Several states even have policies allowing for data exchange agreements that allow IISs to share immunization data across other stakeholders (Hinman et al., 2007) and these agreements can consolidate multiple sources of vaccine information to improve rates (Kempe et al., 2001).

The capabilities of IISs are designed to promote and encourage improvements in immunizations but the effectiveness of IISs in the literature is less clear. This is likely because individual states have a large influence over the effectiveness of their IISs. In the U.S., the Federal government makes immunization recommendations and conducts immunization surveillance nationally, but immunization policies are enacted by State governments. Today, most of the operating IISs are operated by State immunization programs though some larger cities and regions also operate an IIS separately from their state IIS (Centers for Disease Control and Prevention, 2018b). Policies that govern the operation of IISs are complex in design and interpretation, have been described in detail elsewhere (Horlick, Beeler, & Linkins, 2001; Martin, Lowery, Brand, Gold, & Horlick, 2015). These policies include the type of governing authority under which states operate their IIS. States may have an explicit law to operate an IIS or may operate under a more general public health statute by which they extrapolate their authority as a public health interest (Horlick et al., 2001). Additionally, these policies dictate the immunization entities that are mandated to report immunizations to the IIS (if any), the type of patient consent required to include information in the IIS (opt-in, opt-out, or mandatory), and who will have access to this data (authorized access and interoperability laws). While the laws have been described in detail in the IIS literature, there remains a gap in the research examining these laws effects on immunization rates.

Early research examining whether the probability that a child was up-to-date (UTD) on all of their vaccines demonstrated no effect between provider IIS participation and UTD status (Kim, Frimpong, Rivers, & Kronenfeld, 2007; Mennito & Darden, 2010). However it is possible that IISs were not well-established at the time of the studies. Research in Australia demonstrated a 30% increase in overall immunization rates ten years after the implementation of an IIS (Groom et al., 2015). Rates for individual immunizations, such as the seasonal influenza vaccine, showed that IIS utilization to conduct proactive outreach and send vaccine reminders increased immunization rates (Bluml, Brock, Hamstra, & Tonrey, 2017; Dombkowski, Harrington, Dong, & Clark, 2012).

It is possible that progress in improving rates with IISs is slow and that is why previous research did not demonstrate an effect on UTD status and more time is needed. Research so far has not looked at individual vaccine improvements for incremental progress or assessed whether IISs improve the quality of vaccines by reducing the number of invalid doses- doses that are delivered too young or too close together. Several studies have examined invalid doses, though these studies are also quite dated. The rate of invalid doses in U.S. children is around 10%. IISs have the capacity to forecast vaccine needs, using immunization histories housed within the IIS and ACIP recommended guidelines, to support providers at the point of care. Thus far, research has not examined whether IISs are effective at reducing the number of invalid doses.

To support state immunization programs' goals for increasing immunization rates and improving quality using IISs, a series of Functional Standards were developed through a collaboration between the Centers for Disease Control and Prevention (CDC), National Center for Immunizations and Respiratory Diseases (NCIRD), the Immunizations Information Systems Support Branch, IIS managers and other technical experts (Immunization Information Systems

Support Branch within CDC/NCIRD, 2013). These standards promote the utilization of IISs to improve immunization delivery at the point of care, maintain accurate and complete immunization records while maintaining confidentiality, and working with all authorized stakeholders within the purview of state laws and statutes (Immunization Information Systems Support Branch within CDC/NCIRD, 2013). These functional standards offer a framework for IISs to measure their progress and effectiveness, but to date, literature has not measured these functional standards to evaluate IISs.

Research Aims

Vaccines are highly effective at preventing disease which can cause complications such as disability and death (Andre et al., 2008a). Although child immunization rates are relatively high, the U.S. consistently misses its targets and rates show evidence of declines (Hill et al., 2017). These declining rates leave communities vulnerable, with vaccine-preventable disease outbreaks increasing in frequency and size. Since the mid-1990s, numerous investments have been put into the development of IISs to improve immunization rates and help reduce the burden of VPDs (Freeman & DeFriese, 2003; Hinman et al., 2007). Although widespread adoption of IISs by states has occurred, research on their effectiveness at improving the quality and rates of vaccination are unclear.

Proponents of IISs have claimed that IISs have the capacity to improve immunization rates, but only when providers participate and when patient data is sent to the IIS (Clark, Cowan, & Bartlett, 2006; Freeman & DeFriese, 2003). However, early research suggests IIS participation is not associated with improvements in completion rates for the full combined childhood vaccine series (Kim et al., 2007; Mennito & Darden, 2010). Work from Australia suggest this change may occur over a longer period of time, and it is possible (Groom et al., 2015). Few studies have

explored deeper the participation by providers and patients' influences over this participation and utilization of IISs (Kim et al., 2007; Luman, McCauley, Stokley, Chu, & Pickering, 2002). Both provider beliefs and parental characteristics have been associated with improved immunization rates (Kempe et al., 2017; Luman, McCauley, Shefer, & Chu, 2003). And while details about IISs policies are available in the literature (Horlick et al., 2001; Martin et al., 2015), a gap exists in how IIS policies affect immunization rates. Further, studies on IIS utilization and effectiveness are often limited to targeted populations, localized areas, or specific immunization needs, all of which prevents generalizability to the broader population (Groom et al., 2015).

The purpose of this dissertation is to examine relationships between IIS policy and participation on immunizations in pre-school aged children. Throughout this dissertation, I incorporate data from the national, state, provider, and aggregate individual levels to examine the association of IISs with immunizations using three sources of publicly available data from the CDC: The National Immunization Survey (NIS), the Survey of State Immunization Information System Legislation (IIS Leg), and the Immunization Information Systems Annual Reports (IISARs). To address this overarching aim, I conducted three separate studies using the following research aims:

Research Aim 1: Evaluate the relationship between provider participation in an IIS and up-to-date vaccination status for the full combined series of routine vaccines in children aged 19-35 months in the United States.

> *Hypothesis 1:* Children whose providers participate in an IIS have a higher probability of receiving the full combined series of age-recommended vaccines than children whose providers do not participate in an IIS.

Research Aim 2: Examine the relationship between IIS utilization and invalid vaccinations in children 19-35 months of age.

Hypothesis 2: Children whose providers participate in an IIS will have fewer invalid vaccines administered outside of the required age and interval between doses.

Research Aim 3: Analyze the relationship between mandate, consent, and vaccine forecasting as proxies for measuring the IIS functional standards and state up-to-date immunization rates.

Hypothesis 3a: States with full reporting mandates and mandatory consent policies will be associated with higher state UTD rates.

Hypothesis 3b: States that forecasted vaccines to an electronic health record will be associated with higher state UTD rates than states that did not forecast vaccines.

Dissertation Contributions

This dissertation research adds to the growing literature on IIS evaluation by examining the relationships of IISs on vaccination status. This work contributes to the literature in three ways. First, it supports the previous literature in finding no effect of IIS participation on child UTD status but adds new data on the association between IIS participation on invalid doses. Second, this research aligns with previous studies on the effect of mandate and consent types on state immunization rates and adds new findings about the effect of an interaction between mandate type and consent. The finding that states with no provider mandate are associated with higher immunization rates highlights the importance of provider beliefs on immunizations. This dissertation also contributes meaningful data as to the role of states influence on immunizations. States with higher odds of child UTD and lower odds of invalid doses may have policies, programs, and resources that prioritize quality of immunizations over quantity compared with

states that are associated with higher odds of child UTD and higher odds of invalid doses. Finally these studies further highlight the dynamic but important relationships between policy, and participation by providers and parents that can inform future immunization improvement strategies.

Dissertation Organization

This dissertation is organized into six chapters following a hybrid three-essay format. In Chapter 2, I present a review of the literature that provides background information and conceptualizes the impacts IISs have on immunizations, critiques the current research, and identifies the gaps that I will address in the remaining chapters. This literature chapter adds context and background that is not present in the literature sections of the three essays to help the reader understand the structure and function of IISs. In Chapters 3-5, I present my three research essays examining the association of IIS participation on the up-to-date vaccination status in children 19-35 months old (Chapter 3), the relationship between IISs and invalid doses (Chapter 4), and lastly I evaluate the association of IIS policies and provider participation on state-level immunization rates (Chapter 5.). I will then provide concluding remarks and future directions for IIS research in Chapter 6.

Chapter 2 Literature Review

Background

Immunization information systems (IISs) have been widely adopted to increase immunization rates, reduce record fragmentation, and improve the overall quality of vaccines. Research is needed to understand how large investments in immunization information system technologies are generating improvements in vaccine coverage and reducing vaccine preventable diseases that are predicted by theory. Existing studies offer mixed evidence regarding the relationship between IISs, and vaccinations. Several studies find that IISs help improve immunization delivery by improving immunization record keeping and increasing immunization rates through features such as clinical decision support (Bluml et al., 2017; Dayton, 2014; Groom et al., 2015; Zimmerman, Bartlett, Enger, Gosney, & Williams, 2007). Others fail to reject the null of no effect of IIS participation on immunization rates (Kim et al., 2007; Mennito & Darden, 2010).

Several gaps exist in current IIS evaluative research. There is a dearth of literature on the effects between state IIS policies on immunization rates. Functional standards have been designed to promote the utilization of IISs to improve immunization rates and help programs measure the effectiveness of IISs, yet research on how well IISs achieve these functional standards is remarkably absent. In the following paragraphs, I provide the background on immunization information systems and their relationship to vaccine-preventable diseases to better understand how they can function to improve immunization rates and quality of vaccines administered, as well as identify gaps in the current research.

Links Between Vaccinations and Vaccine-preventable Diseases

Vaccinations are one of the greatest public health achievements (Control & Prevention, 2011). Widespread adoption of vaccines has led to dramatic decreases in morbidity and mortality

worldwide. Although there has been more than a 99% decrease in disease and deaths attributable to these diseases (Roush & Murphy, 2007). However, recent evidence suggests that immunization rates are declining (Hill et al., 2017), and vaccine-preventable disease outbreaks are increasing in frequency and size (Gahr et al., 2014). Contributors to these low rates include record fragmentation and incomplete vaccination histories, the inability to determine vaccination needs, and rising prevalence of vaccine hesitancy (Larson, Jarrett, Eckersberger, Smith, & Paterson, 2014; Stokley et al., 2001).

Currently, the ACIP recommends vaccines to protect children against 16 vaccine-preventable diseases (Centers for Disease Control & Prevention, 2015a). The age and timing of immunization is important to maximize the protective benefits of vaccination. The complex childhood vaccination schedule increases the difficulty in tracking immunization status by providers and parents and increases the likelihood of missed opportunities or receiving inappropriate doses (Feikema et al., 2000; Luman et al., 2002). Additionally, children frequently have multiple providers or receive immunization outside of their primary care provider's office which leads to fragmented records (Freeman & DeFriese, 2003; Yusuf et al., 2002). To increase immunization rates, it is important to have a system that can track immunizations across providers and provide real-time immunization histories (Gostin & Lazzarini, 1995). The use of immunization information systems is one strategy that has the potential to achieve these benefits and to improve immunization rates.

Operation of IISs

In the U.S., IISs are operationalized primarily at the state level and are governed by a variety of state laws and statutes (Martin et al., 2015). As a result, state IISs are at various stages of maturation which affects how they perform and function. Although states have varying

priorities, a series of functional standards guide state immunization programs on how to maximize the benefits of the IIS and provide a framework for evaluation (Immunization Information Systems Support Branch within CDC/NCIRD, 2013). Generally, there are six functional standards that IISs strive to achieve:

1. Support the delivery of clinical immunization services at the point of immunization.
2. Support the activities and requirements for publicly-purchased vaccine, including the Vaccines For Children (VFC) and state purchase programs.
3. Maintain data quality (accurate, completely, timely data) on all immunization and demographic information in the IIS.
4. Preserve the integrity, security, availability and privacy of all personally-identifiable health and demographic data in the IIS.
5. Provide immunization information to all authorized stakeholders.
6. Promote vaccine safety in public and private provider settings.

Operationally, IISs contain a list of core data elements that are suggested for collection (Centers for Disease Control and Prevention, 2013). Examples of the types of data include patient-specific information (e.g. name, address, birth date, birth facility, demographics and other identifiers, historical vaccine/disease data), vaccine-specific information (e.g. manufacturer, lot number, expiration date), and vaccine-administration information (e.g. site of delivery, date of administration, vaccine information statement version number) and provider-specific information (e.g. provider facility, ordering providers, administering provider)(Immunization Information Systems Support Branch within CDC/NCIRD, 2013). The core data elements are critical for information data exchange, for example, when multiple records from different systems are being

merged or transferred to a new system. The core data elements are also vital for ensuring complete and accurate records in the IIS.

IISs consolidate immunization records to improve immunization rates

Historically, there has never been a standardized way to document, track, and access vaccination information in the U.S. leading to fragmented or scattered records (Yusuf et al., 2002). Fragmentation of immunization records across multiple providers led to the administration of vaccines at inappropriate ages or intervals between doses, extra immunizations, or allowed for completely missed opportunities for vaccination (Feikema et al., 2000; Stokley et al., 2001; Yusuf et al., 2002) and is considered a barrier to completion of the immunization series (Klevens & Luman, 2001).

While electronic medical records have standardized documentation practices for vaccinations, they did not fix the problem of record scattering or fragmentation. Many children have multiple immunization providers (Yusuf et al., 2002). In a rapidly changing vaccine delivery system, the likelihood of multiple providers is increasing with the ability to now receive vaccines from school settings, pharmacies, or other wellness clinics (Orenstein et al., 2005). Additionally, Americans today are increasingly mobile thereby creating fragmentation of medical records if records are not migrated to the new location (Stokley et al., 2001). In one study, 30% of children who were not up-to-date on their vaccines had changed providers since birth (Freeman & DeFriese, 2003) highlighting the impact of record fragmentation on immunization rates.

Today's immunization information systems (IISs) are confidential, centralized, electronic hubs that house immunization data and offer additional functionality to serve immunization programs (Centers for Disease Control & Prevention, 2013). IISs consolidate demographic

information and immunization records, from all sources (e.g. pharmacies, vital statistics, etc.) while maintaining patient privacy and confidentiality (Hendrickson, Panchanathan, & Petitti, 2015; Wood, Saarlas, Inkelas, & Matyas, 1999) addressing the problem of record scattering and fragmentation. Multiple sources of vaccine information have been linked with higher accuracy of immunization histories and are more likely to result in complete records (Davidson et al., 2003; Hendrickson et al., 2015). However, systems may not be linked to other data sources (Dayton, 2014). Concerns over data accuracy have arisen over record duplications because of data mismatches (Davidson et al., 2003; Hendrickson et al., 2015).

IISs rely on data submitted by participating providers electronically, or in some cases, by hard copy (e.g. paper records, faxed documents, etc.) (Hinman & Ross, 2010; "Progress in development of immunization registries--United States, 1999," 2000). When a provider enters a dose on a patient into the EHR, that information is sent either in real-time or batched at specific times to the IIS (Martin et al., 2015). For many IISs, this electronic linkage was unidirectional meaning data went from EHR to IIS, but providers were not always able to retrieve the vaccine information from the IIS (Murthy, Rodgers, Pabst, Fiebelkorn, & Ng, 2017).

State-wide IISs will not completely solve the problem of fragmented records since they are limited to the state where they operate. Currently, there are no plans for a nationally linked IIS due to differences in policies and laws surrounding privacy, consent, and data collection.

IISs improve rates by supporting providers at the point of care

IISs can also improve rates by supporting providers at the point of care using clinical decision support tools. As IISs were further developed, a bi-directional communication pathway was created that allowed other providers, health officials, or school nurses to query the system to obtain a vaccination record or retrieve a vaccine forecast that recommended vaccines that were

"due" for a specific patient (Immunization Information Systems Support Branch within CDC/NCIRD, 2013). This enables providers to provide appropriate vaccinations and reduces errors in vaccine administration or prevents a missed opportunity to vaccinate (Freeman & DeFriese, 2003). Due to the complexity and expanding ACIP schedule of routine vaccines, the clinical decision support feature helps physicians choose the appropriate vaccine at the right time for a specific patient.

It has been difficult to evaluate how well these features work due to the inability to conduct evaluations at the clinical sites on how providers utilize IIS features (Groom et al., 2015). Additionally, not every IIS has forecasting capabilities which further limits evaluation. Few studies have examined clinical decision support tools in proactive influenza campaigns and demonstrated improvements in immunization rates (Bluml et al., 2017; Zimmerman et al., 2007). These studies, however, did not look at complex vaccine series and were conducted in adult populations. In theory, by offering a centralized hub for immunization data, public health officials, providers, and other stakeholders can actively monitor immunizations, deliver better patient care, and use the information in the IIS to improve the overall immunization program.

IIS policies can influence participation and overall immunization rates

Every state that operates an IIS has policies that dictate the capabilities, participation, and utilization of the vaccine information. The type of authority that states use to operate an IIS vary among the states from being explicit about operating an IIS to the operation of one under an assumption of a public health statute (Horlick et al., 2001). In addition to the authority are policies that dictate participation in the IIS. Mandates for reporting immunizations to the IIS affect providers, pharmacies, and other facilities that administer immunizations (Centers for Disease Control & Prevention, 2015b; Madewell et al., 2017). They may be full mandates that

apply to all facilities and all age groups, or they may specify restrictions that only apply to some facilities or providers, such as those who participate in the VFC program, or to specific age groups (e.g. children under 6 years, or all ages) (Centers for Disease Control & Prevention, 2015b).

Participation also extends to those patients who have their data in an IIS which is determined often by the IIS consent policy. Some states have an explicit consent process which requires patients to actively opt-in to having their vaccines submitted to the IIS. This requires recruitment of patients, often by the participating providers, who would have to educate and provide informed consent to patients prior to submitting data (Berry et al., 2013; Boom, Sahni, Nelson, Dragsbaek, & Franzini, 2010). Other states use an implicit consent process which is an implied consent that automatically opts patients into the IIS. They are still educated and notified of the IIS, and in some cases, are given information on how to opt-out should they wish to have their data excluded from the IIS (Berry et al., 2013; Hedden, Jessop, & Field, 2012). However, there are states that mandate patient participation in an IIS with no ability to opt out with the rationale that vaccinations are a public health issue and included in statutes that govern other public health data in the state.

Finally, data sharing policies and interoperability are a critical component in the operation and success of an IIS. The presence of data in an IIS is not useful if there is no access or policy for using or sharing the data with other immunization stakeholders (e.g. other providers who may need records) (Hendrickson et al., 2015; Hinman et al., 2007). States determine which users can have access to the data, and what type of access they will have (read-only or capable of making changes to the information) (Centers for Disease Control and Prevention, 2018b). Additionally, states will sometimes have agreements with other IISs for data-sharing, but these

agreements are complicated by differences in confidential data-sharing laws and privacy of health data through Health Information Portability and Accountability Act (HIPAA) (Freeman & DeFriese, 2003; Hendrickson et al., 2015).

The policies mentioned above have been well-documented in the literature and updated over time to reflect policy changes (Hedden et al., 2012; Horlick et al., 2001; Martin et al., 2015), however, there has been little research about how these policies that govern the operation of an IIS affect immunization rates. Madewell et. al., (2017) states that provider participation will be lower in the presence of a reporting mandate, yet another group says that mandates are required for increasing provider participation (Groom et al., 2015). Consent policies are a little clearer in the literature. Participation will be higher with implicit or mandate policies and lower with explicit opt-in policies that require extra steps by the patients to opt-in (Berry et al., 2013; Boom et al., 2010). Studies have not examined the effects of these policies on actual participation, highlighting an important gap in the literature and for policymakers considering other policy types for their state IISs.

The gaps identified throughout this review serve as the impetus for the research aims outlined in Chapter 1. This dissertation will address the IIS literature by examining the relationship between IIS participation on child UTD status, IIS participation on invalid doses, and IIS policies and provider participation on state UTD rates in the next three chapters.

Chapter 3 Immunization Information Systems' and the Association with Up-to-Date Status in U.S. Children 19-35 Months of Age

Introduction

Vaccines are widely accepted as safe and cost-effective strategies for preventing the contraction and spread of vaccine-preventable diseases (VPDs). In many cases, morbidity and mortality have been reduced by as much as 99% (Andre et al., 2008b; Roush & Murphy, 2007), and rates for individual vaccines have remained "high and stable" (Hill et al., 2015) over the last decade. However, as successful as vaccines have been, in order to maintain the protection against VPDs, high rates of vaccination must be sustained (Brunson, 2013). Evidence that protection may not be at optimal levels remains present throughout the United States (Diekema, 2012).

Several recent examples of outbreaks in the U.S. have demonstrated the vulnerability of under-protected populations. Between 2001 and 2015, more than 1,789 confirmed measles were recorded and at least 70% of those occurred in unvaccinated individuals (Clemmons, Wallace, Patel, & Gastañaduy, 2017). The multi-state outbreak of measles originating in a crowded theme park in 2016 demonstrated the speed and mobility of a highly contagious infection to spread throughout an under-protected population (Chemerinsky & Goodwin, 2016). In 88% of those confirmed cases (110/125), patients were either unvaccinated or had an unknown vaccination status (Porteous et al., 2016) and the close contact within a crowd further increased the risk of spreading the disease. In 2017, Minnesota experienced an outbreak of measles with 75 confirmed cases including at least 20 hospitalizations (Hall et al., 2017; Minnesota Department of Health [MDH], 2018). Ninety-five percent of those cases were in unvaccinated people (Hall et al., 2017). That outbreak also demonstrated the capacity for these diseases to cause serious illness in modern day society. Outbreaks have not been strictly due to measles; the number of pertussis cases is also increasing even after accounting for the natural cyclical incidence of the pertussis organism (Carrico & O'keefe, 2013; Cherry, 2012). In 2014, California documented 10,831 cases

of pertussis including two infant deaths and hundreds of hospitalizations (Minnesota Department of Health [MDH], 2018).

In these examples, most infected patients were unvaccinated, though it remains unclear how many were simply under-vaccinated, or were not able to be vaccinated, and how many infections could have been prevented. While the U.S. has been successful in achieving relatively high rates of vaccination (Hill et al., 2015) these outbreaks have been associated in the literature with decreases in vaccination (Aloe, Kulldorff, & Bloom, 2017) and provides the impetus for further investigation into the vaccination status of the U.S. population.

The U.S. national vaccine program has different recommendations for vaccination dependent upon age, health status, and other risk factors. Children are frequently the focus of vaccination efforts to increase vaccine uptake for several reasons. First, they represent a vulnerable population as their immune systems are not fully mature (McDade, 2003) placing them at increased risk of infection and complications. Often, people with immune system defects are identified in early childhood and represent a smaller population who should not be vaccinated with certain types of vaccines (Cooper, Pommering, & Koranyi, 2003; Rubin et al., 2013). These children rely on herd immunity for protection against those diseases where vaccines are contraindicated. Second, the majority of routine childhood immunizations are given in the first three years of life and it can be challenging for parents to adhere to an increasingly complex vaccination schedule thus reducing the likelihood that a child receives all of the necessary doses for full protection (Zell, Ezzati-Rice, Battaglia, & Wright, 2000). Third, when un-vaccinated children reach school-aged they may become carriers for these infections which places classmates, younger children in day cares, grandparents, and other potentially vulnerable people at risk for contracting serious infections (Salmon et al., 2005).

The progress of the U.S. national immunization program is measured in part by estimating rates of vaccine completion (Murray & Frenk, 2000). The Advisory Committee on Immunization Practices (ACIP) is a group of leading experts on immunizations who evaluate the scientific evidence pertaining to the safety and effectiveness of vaccines (Centers for Disease Control & Prevention [CDC], 2016). They release updated schedules which recommend the type, number, spacing, and ages for each dose of a vaccine that would be required for a child to be optimally protected (Ahmed, Temte, Campos-Outcalt, Schünemann, & ACIP Evidence Based Recommendations, 2011). These recommendations are available publicly, along with information about the vaccines themselves so that parents and providers can make informed choices. The immunization schedule represents the standard by which vaccination progress is measured.

In the U.S., immunization information is collected using the National Immunization Survey (NIS), the current gold-standard since 1994 for estimating vaccination rates (Zell et al., 2000). This two-part survey culminates with the collection of immunization data on age-eligible children whose households were selected for participation. The information is submitted by a child's vaccination providers and, following a complex survey design, is weighted to be representative of the population of children in target age ranges (e.g., 19-35 months, 4-6 years, etc.). Rates derived from the NIS are used to measure progress toward achieving the Healthy People 2020 immunization objectives (US Department of Health and Human Services, 2011a). When comparing the NIS vaccination rates published in an annual Morbidity and Mortality Weekly Report (MMWR), the U.S. consistently fails to reach the immunization targets of 90% for individual vaccines and 80% for the routine full combined series by the age of three years

(US Department of Health and Human Services, 2011c). This has motivated the public health community to improve the national rates.

Multiple strategies have been utilized to improve vaccination rates in children since the Healthy People initiative began publishing immunization goals in 1979 (United States Department of Health Education Welfare, 1979). Aggressive campaigns were created for increasing vaccine awareness, acceptance, and uptake. Programs to improve access to vaccines at lower out of pocket costs, such as the Vaccines For Children (VFC) program and a preventive health mandate in the Affordable Care Act which included vaccines at no out of pocket costs, have helped families throughout the U.S. (Koh & Sebelius, 2010; Lee et al., 2007). Additionally, stricter requirements for school entry motivated many parents to get their children up-to-date on their vaccines (Orenstein & Hinman, 1999). To help parents with the complicated vaccine schedule, provider-based reminder/recall systems were able to inform parents when their children were due for a vaccination (Freeman & DeFriese, 2003).

Even though efforts to improve vaccination rates have been somewhat successful, progress has been attenuated by several threats to vaccine uptake which have simultaneously gained momentum in recent years. Currently, there is no real-time and precise method to determine vaccination rates, or gaps of unvaccinated within a community which would allow public health officials and clinicians to target immunization interventions (Freeman & DeFriese, 2003). Estimated rates are only reliable at a national level and may not represent the true coverage within a community and potentially increases the risk for outbreaks of VPDs in communities that are not fully protected (Luman et al., 2002).

It is important to mention these challenges that public health officials face because it helps to explain why achieving target vaccination rates remains elusive. First, parental and

provider vaccine hesitancy is increasing in the U.S. with many parents perceiving the risks of vaccination greater than the risk of the disease it prevents (Chatterjee & O'Keefe, 2010; Smith et al., 2011). Though risks of contracting a VPD may be low within a person's community, the increasing mobility of society has led to an increase in outbreaks due to importation of an infection. Importation of an infection into an under-protected community has the potential to be catastrophic (Boggild et al., 2010; Gushulak & MacPherson, 2004). Second, the reduced incidence rate of VPDs has led to a generation of providers' who lack experience in identifying and treating vaccine-preventable infections (Brookes, 2017; Chatterjee & O'Keefe, 2010). Third, safety-conscious parents concerned with the number of vaccines recommended at a single visit have sought providers willing to provide an alternative vaccination schedule, which arbitrarily spaces vaccines out over more time and additional visits (Offit & Moser, 2009; Pediatrics, 2012). However, these alternative schedules only serve to delay vaccinations and the safety and efficacy has not been supported by the literature at this time (American Academy of Pediatrics, 2008). Finally, children are more likely to have multiple providers (National Center for Immunization and Respiratory Diseases, 2017; Stokley et al., 2001), which in the absence of a universal electronic health record, creates the potential for fragmented vaccine records and raises questions about the true vaccination status for the child.

One strategy to improve rates that is gaining national traction are the use of Immunization Information Systems (IISs) or immunization registries. An Immunization Information System is an electronic repository that has the capability of housing all the specifics of a given vaccine dose in a population-based database (Groom et al., 2015). IISs rely on participating providers to supply vaccination data electronically. When a vaccine is given to a patient, the information is sent either in real-time, or batched at specific times, as an upload to the IIS (Martin et al., 2015).

IISs also contain a feature which can recommend or forecast vaccines for a specific patient, provided they are in the IIS database, according to the ACIP schedule for that child's age and history of vaccination (Groom et al., 2015). Depending on the data sharing and query capabilities of the IIS and facility, other providers, health officials, or school nurses, with consent, can query the system providing a bi-directional unified flow of vaccine information which would ideally lead to improved adherence, documentation, tracking and rates of vaccination.

The real-time capability could also allow public health officials to use geographical coding to look at localized immunization rates in specified areas for targeted interventions or outbreak investigations if data quality and assurance could be optimized. Additionally, it could potentially solve the problem of record scattering (Martin et al., 2015) since the IIS houses all vaccine information on a specific patient which was uploaded by participating providers. This means for example, that if a child has four immunization providers and all are participating in an IIS, they would be able to receive the vaccine information from each other using a single query and without the need for their EMRs to be directly linked. A potential drawback remains if a child were to leave the catchment area of the IIS, which frequently happens when children move out of state.

Though IISs have been stated as a proven strategy for improving immunization rates, and large investments have been made by states' and the federal government (Freeman & DeFriese, 2003; Rask, Wells, Kohler, Rust, & Cangialose, 2000), there is a paucity of research regarding the effect IISs have had on immunization rates. There is currently no national IIS since immunization programs are implemented at the state level, but there are 55 IISs operating at state, local, and regional scopes (Murthy et al., 2017). These independent IISs can capture and coordinate records within a state or region but sharing information between these IISs is

complicated by the various state laws and statutes that govern their operation (Groom et al., 2015; Martin et al., 2015), and thus leaves the U.S. without a linked system for vaccine tracking. The interoperability of IISs is outside the scope of this paper and is covered elsewhere in this dissertation.

There has been little research specifically on the role that provider's participation in an IIS has on the impact on childhood vaccinations. The goal of this chapter is to evaluate the relationship between provider participation in an IIS and up-to-date vaccination status for the full combined series of routine vaccines in children aged 19-35 months in the United States.

Conceptual Framework

Vaccination policies occur at the national and state-levels in the U.S., while vaccine uptake results from a series of complex and dynamic relationships between public health entities, providers, and parents. To guide my research, I developed a conceptual framework (Figure 3.1) that depicts the most important relationships relevant to childhood vaccination status. In this paper, child's vaccination status will be measured by whether a child is fully up-to-date on the full combined series of routine vaccinations recommended by the ACIP which is determined at a national level in the U.S. Specifically, I am interested in the relationship between provider participation in an IIS and the likelihood that a child has received the full series of recommended vaccines, also known as being up-to-date (UTD). In my model, I include child characteristics as controls, as well as maternal characteristics since a child's mother is often the most influential person in vaccine decision-making, I include characteristics that are potential influencers of the mother's knowledge and behavior since this cannot be directly measured by this dataset. Finally, as my predictor of interest, I include a variable that proxies for provider participation in an IIS.

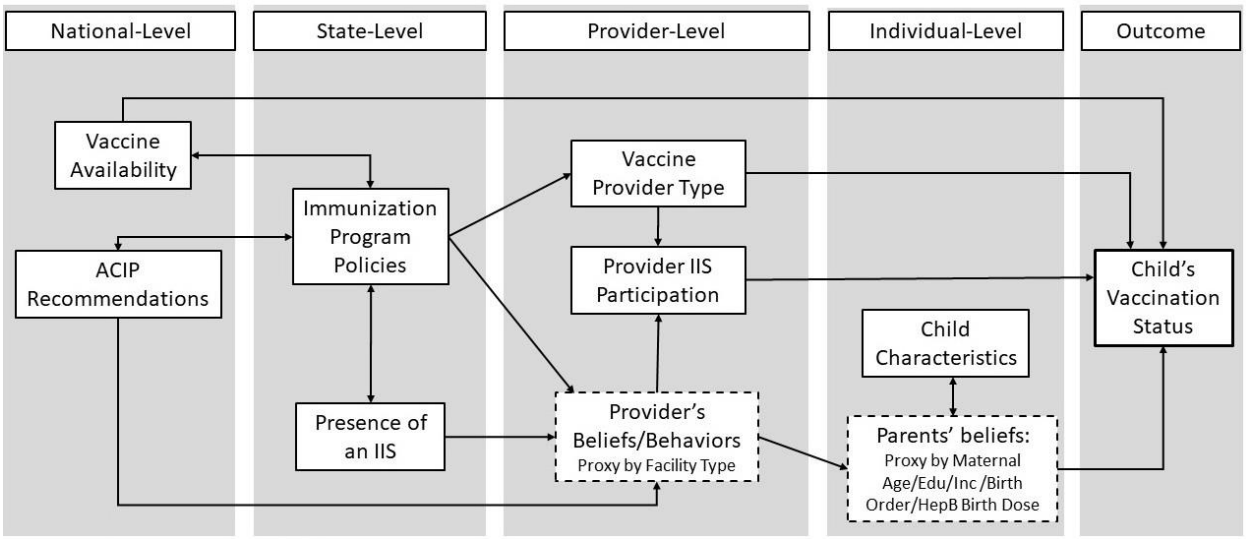


Figure 3.1 Conceptual Framework for Child Vaccination Status

Methods

Data source. The National Immunization Survey data is collected through a two-phase process described in detail in the literature (Smith et al., 2001; Zell et al., 2000) and throughout this dissertation. The first phase is intended to identify households with children in the targeted age range of 19-35 months during the 2016 calendar year. The NIS uses random-digit dialing survey (RDD) and a dual-frame design that encompasses sampling techniques for both telephone landlines and mobile numbers due to the decrease utilization of household landlines. During the first phase, demographic information and some vaccine information is collected from the person in the household most knowledgeable about vaccines for the child- typically a parent or guardian; most frequently the mother is the respondent (National Center for Immunization and Respiratory Diseases, 2017). During this phase, the parent/guardian is asked to identify all the child's immunization providers and consent is obtained to contact those providers and request the immunization records.

The second phase of the NIS, the provider record check study, a survey is mailed to all of the identified providers for the eligible child(ren) identified in phase I. Providers are asked to list all vaccines in a child's record, type, and date given so that an age for each dose can be calculated.

Study sample. Children ages 19 to 35 months of age in the 2016 National Immunization Survey data set in the fifty states and Washington, D.C. with adequate provider data are included in this study (N = 14,988). Adequate provider data is defined as one or more vaccine providers who report immunization data on a child during the provider-record check portion of the NIS. Children who are unvaccinated are also considered to have adequate provider data if a provider is identified by the parents and the provider responded with "child has received no vaccines". I exclude Puerto Rico and other territories since I am interested in understanding the effect of participation in IIS within the states and information about how IIS operate in Puerto Rico, if any, is not within the scope of this research. I also exclude children who are missing values for the registry variable (N = 237) for a final sample size of N = 14,751.

Design. In this study, I analyze the relationship between the up-to-date vaccination status and whether the provider reported a participant child's vaccination data to an IIS. I conduct a secondary analysis using the 2016 NIS. Survey weights (Dual-Frame RDD weights) are utilized for the summary statistics and Chi-squared analyses to examine bi-variate relationships. Provider weights are suggested in the NIS Data User Guide for conducting immunization assessments on children with adequate provider data and are utilized in the regression analyses (National Center for Immunization and Respiratory Diseases, 2017). The complex survey design makes the dataset representative of the U.S. population of 19-35 months old children. Lastly, to examine

the effect of registry participation on UTD status, I use a logistic regression model that is guided by the conceptual framework.

Dependent variable. For this analysis, the dependent variable is a dichotomous up-to-date (UTD) indicator for whether a child received the full combined series of ACIP routinely recommended vaccines. This series includes 4 DTaP, 3 Polio, 1 MMR, 3 Hib, 3 HepB, 1 Var, and 4 PCV doses by 35 months of age (Hill et al., 2015), also known as the 4:3:1:3:3:1:4 series, hereafter referred to as the full combined series. I examine the full series of routinely recommended vaccines since it is the most representative of a child's overall protection against vaccine preventable diseases and is the series recommended for school entry.

Independent variables. The independent variable of interest is whether a child's data was submitted to a registry or IIS by their providers. This data is collected in response to a question on the provider record check survey in phase II of the NIS and is proxying for provider participation in an IIS or registry. This categorical variable is re-coded as No Participation if the child is recorded as "None" of the child's providers submitted the immunization information to an IIS, Any Participation if the child is recorded as having "Some but possibly or definitely not all", or "All of the providers" submitted to an IIS, and Unknown Participation for children whose providers marked "Unknown" when asked if child's records were submitted to an IIS.

Provider characteristics. This dataset does not capture much information about the provider, however, the type of provider(s) a child has (e.g. All public, All private, All hospital) is included and is used to proxy for provider's beliefs since providers choose their type of practice which is potentially influenced by their beliefs. For example, public providers are more likely to participate in federal vaccine funding programs and may be more likely to administer immunizations than private providers (Mennito & Darden, 2010). In the provider-record check

portion of the survey, providers self-identify the type of facility they practice in (Centers for Disease Control and Prevention, 2016). Providers may select multiple choices from the facility type including private (solo, group, or health maintenance organization), hospital-based clinic, public health clinic, military hospital, various health centers (migrant, rural, community), and other facilities such as pharmacies, Women, Infants, and Children, and school-based clinics. I make the assumption that all public-health clinics, including rural and community health centers, are categorized as public facilities, hospital-based clinics as hospital facilities. Those that do not fit into the criteria of public, private, or hospital, (e.g. pharmacies) are assumed to be categorized in the Military/Other category. The provider type variable is re-coded and aggregated at the child level in the public-use data file and prevents analyses of individual providers.

State-level influence. Current state of residence is included to help control for state-level immunization policies. There are currently no national laws, however, the ACIP makes national recommendations which are then carried out by state immunization programs. These immunization policies also affect state-run IIS and may influence provider behavior. Additionally, I include a variable that assesses mobility measured by whether a child currently lives in a different state from where they were born to adjust for state selection effects of vaccination history

Maternal characteristics. Previous literature on vaccination behaviors suggests that mothers are the most influential person in childhood vaccination decisions (Luman et al., 2003); their attitudes toward vaccination were significantly predictive of infant vaccination status (Fadel et al., 2017). There is no direct way to measure maternal beliefs and behavior, so I proxied for it in several ways. I select variables that have been identified in the literature as influential on a mother's vaccine knowledge and decision-making (Luman et al., 2003) including: maternal age,

maternal education, a household income and poverty variable, and whether a child received a birth dose of Hep B vaccine.

Younger maternal age has been associated with lower child vaccination rates (Luman et al., 2003), so controlling for maternal age (≤ 29 yrs or > 29 yrs) is important when evaluating the effect of IIS on rates. The effect of maternal education is less clear on child vaccination status. For example, older studies have shown that advanced maternal education is associated with higher rates of childhood vaccinations (Luman et al., 2003), however, more recent studies have shown there are clusters of individuals with college education who are less accepting of vaccines (Healy & Pickering, 2011). Therefore, I include maternal education (< 12yrs, 12 yrs, > 12 yrs-non-college grad, College Grad) as a control to help improve the fit of the model.

Disparities in vaccination rates have also been identified based on socio-economic status (Reich, 2014), therefore, I include a poverty status variable, available for all children, that is based on the 2011 through 2015 Census data for poverty thresholds (Centers for Disease Control & Prevention, 2017). This variable is coded as "below poverty", "above poverty but less than $75k" and "above poverty and more than $75k" and an "unknown/refused to answer" group. Poverty thresholds are determined annually using the using data from the Census Bureau (National Center for Immunization and Respiratory Diseases, 2017). I control for year fixed effects in my models to adjust for the annual change. Finally, the birth dose of Hep B may proxy for maternal beliefs and behaviors towards vaccination and has been used elsewhere in the literature as a covariate or control (Mennito & Darden, 2010; Yusuf, Daniels, Smith, Coronado, & Rodewald, 2000). Accepting the birth dose of Hep B might provide insight to the maternal beliefs about vaccination at a critical time in parent and child-development.

Child characteristics. Child characteristics are included in the model as controls. The ACIP recommendations for the full series of routine vaccination, excluding the annual vaccines for Flu prevention and the Rotavirus series, to be completed by 18 months of age, therefore, this sample of 19-35 months of age old children should all have completed the series at the time of data collection (Zell et al., 2000). I use child age group in months (19-23, 24-29, 30-35), gender (Male/Female) and race/ethnicity (Black, Hispanic, White, Multiple/Other) as controls. I include the child's race/ethnicity as a control in the model since there are known disparities in the immunization rates for vulnerable populations which are typically racially diverse (Hill et al., 2015). Lastly, I include an indicator for first-born status (Yes/No) because children at lower birth orders are more likely to be UTD (Brenner, Simons-Morton, Bhaskar, Das, & Clemens, 2001).

Analysis. ***Bivariate Statistics.*** First, to look for potential sources of selection bias, I conduct a series of corrected, weighted Pearson chi-square statistics or design-based F statistics to determine statistical significance ($\alpha = .05$). In Table 3.1, I use the survey tabulate function in Stata to obtain design-based F statistics for the variables in my regression model while accommodating for the complex survey design (Kreuter & Valliant, 2007) to compare those children whose providers answered the provider-check portion of the NIS (those with adequate provider data) using provider survey weights, to those who did not have adequate provider data and therefore, no vaccine information. This allows for evaluation of differences in those who are included in the dataset and those who are excluded. Provider information is not available since one of the comparison groups did not complete the provider record check portion of the survey.

Table 3.2 presents bivariate statistics comparing children's provider IIS participation so that any differences can be attributed to IIS participation and not because of differences in participation levels. Finally, I use bivariate statistics to test for relationships between 1) the

dependent variable (UTD status) and independent variables, and 2) multicollinearity between that may bias regression coefficients.

Regression Analysis. To address the main research question, I analyze the 2016 NIS data using a logistic regression model and cluster the error terms at the state-level, as described previously (Cameron & Miller, 2015), and report the adjusted Odds Ratios (aOR) in Table 3.3. These states' fixed-effects treat all data within a state the same with respect to unobserved variables such as state immunization policies. The full model for the regression analysis, based upon my conceptual framework, is shown below. All variables in the model are categorical with variables in bold representing categorical variables with more than two levels.

$$\underline{\text{Full Model}}: \text{utdstat}_i = \beta_0 + \beta_1 * \mathbf{IISParticipation_{i1}} + \beta_2 * \mathbf{State_{i2}} + \beta_3 * \mathbf{ProviderType_{i3}} + \beta_4 * \text{Mobility}_{i4} + \beta_5 * \text{MaternalAge}_{i5} + \beta_6 * \mathbf{MaternalEducation_{i6}} + \beta_7 * \mathbf{IncPov_{i7}} + \beta_8 * \mathbf{ChildAge_{i8}} + \beta_9 * \text{Gender}_{i9} + \beta_{10} * \mathbf{ChildRace/Ethnicity_{i10}} + \beta_{11} * \text{First-born}_{i11} + \varepsilon_i$$

where utdstat is the dependent dichotomous variable for UTD status and β_0 is the probability that a child is UTD holding all other variables constant at zero. Provider-level variables include IIS Participation as the indicator for provider participation in an IIS and ProviderType as the facility type(s) that the child's provider(s) are employed within. Maternal factors include the MaternalAge, MaternalEducation, and IncPov, a measure of income and poverty threshold. Child factors included as controls are ChildAge group, ChildRace/Ethnicity, child Gender, first-born status, and a Mobility variable to indicate if a child has moved from their birth state. State is also included as a geographic control since immunization programs are implemented at the state level and this chapter examines state-level IISs.

Results

Summary statistics. Table 3.1 includes the weighted proportions, using the dual-frame sampling weights, for the full sample, those with adequate provider data, and those without adequate provider data. State-level data can be found in Appendix A.

Children with adequate provider data did not have statistically significant differences from those without adequate provider data by child age group ($p = .85$), child gender ($p = .11$), or first-born status ($p = .67$). There are statistically significant differences by child race/ethnicity ($p = .004$) and whether the children were living in a state different from where they were born ($p = .026$). Children who are White or Multiple/Other race/ethnicities have higher rates of representation in children with adequate provider data (47.9% and 14.1% respectively) than those without adequate data (44.6% and 13.5%); however, the reverse pattern is seen for Black and Hispanic children. Black children represent 14.6% and Hispanic children 27.3% of children without adequate data compared to the 12.1% and 25.9% respectively for children with adequate data.

Maternal age group does not differ significantly ($p = .71$) but maternal education ($p = .009$) and poverty status ($p < .001$) are associated with statistically significant differences between children with and without adequate provider data. There is a higher proportion of

Table 3.1 Summary Statistics of Sample by Adequate Provider Data Status

	Full Sample	With Adequate Provider Data	Without Adequate Provider Data	*p*
Child Age Group (Months)				.85
19-23	30.3%	30.3%	30.2%	
24-29	33.9	34.2	33.7	
30-35	35.8	35.5	36.1	
Child Gender				.11
Male	51.2	50.3	52.1	
Female	48.8	49.7	47.9	
Child Race/Ethnicity				.004
Black	13.3	12.1	14.6	
Hispanic	26.6	25.9	27.3	
Other/ Multiple	13.8	14.1	13.5	
White	46.3	47.9	44.6	
Child First-born Status				.67
No	59.9	60.1	59.7	
Yes	40.1	39.9	40.3	
Moved from birth state				.026
No	88.6	89.3	87.8	
Yes	11.4	10.7	12.2	
Maternal Age (Years)				.71
≤ 29 years	38.3	38.5	38.1	
> 29 years	61.7	61.5	61.9	
Maternal Education				.009
< 12 years (no HS degree)	14.8	16.0	13.3	
12 years (HS degree)	25.8	25.3	26.4	
> 12 years, no college degree	23.0	22.1	24.0	
> College Graduate	36.4	36.6	36.3	
Income/Poverty Status				< .001
Above Poverty, > $75k	30.7	31.3	30.0	
Above Poverty, ≤ $75k	33.3	32.5	34.4	
Below Poverty	29.0	31.2	26.4	
Unknown	7.0	5.0	9.2	
Provider Type[i]				N/A
All Public		12.8		
All Hospitals		13.6		
All Private		55.8		
All Military/Other		2.4		
Mixed		13.9		
Did not answer (Left Blank)		1.5		
Providers submit to IIS[i]				N/A
None		9.4		
Some, but not all		7.3		
All		67.7		
Unknown/Unsure		14.1		
Did not answer (Left Blank)		1.5		
	N = 27,455	**N = 14,988**	**N = 12,467**	

Dual-frame RDD sample weights were used to calculate summary statistics.

i. Only available for those who have adequate provider data since this is collected during the Phase 2: Provider Record Check Survey; aggregated at child-level

mothers with less than a high school education in the adequate provider data sample (16.0 vs 13.3%) and a higher proportion of high school graduates with some college but no degree in the sample without adequate provider data group compared to the adequate provider data group (24.0 vs 22.1%). Poverty levels are different among the two groups as well. Households who did not report their income were present in higher proportions of the sample without adequate provider data (9.2% of the sample compared to 5.0% of those with adequate data) and those reporting incomes below the poverty level represented a higher proportion of those in the sample with adequate provider data (31.2% vs 26.4%).

For children with adequate provider data, I compare the child, maternal, geographic, and provider variables by IIS participation in Table 3.2 to evaluate whether IIS participation varies for the independent variables. No variation in IIS participation is noted based on child age group ($p = .05$), first-born status ($p = .10$), or whether children live in a different state from where they were born ($p = .26$). However, differences are demonstrated for child gender ($p = .04$), and child race/ethnicity ($p < .001$), maternal age and education ($p = .03$ and $p < .001$ respectively), poverty status ($p < .001$), provider facility type ($p < .001$) and for state of residence ($p < .001$) (state data not shown but available in Appendix B).

When testing the relationship between variables, I find a statistically significant relationship between UTD status and IIS participation ($p < .001$). As a check for robustness, I also test IIS participation as a dichotomous categorical variable (recoding the "Unknown" categorized as missing data) to show that the statistical significance remains regardless of how the registry participation is categorized (not shown). Tests for multi-collinearity between the independent variables in the

Table 3.2 Chi-squared Statistics of IIS Participation by Child, Maternal, and Provider Characteristics

	IIS Participation			
	None	**Some/ All**	**Unknown**	***p***
Child Age Group (months)				.05
19-23	3.3%	22.1%	4.9%	
24-29	3.0	26.7	4.2	
30-35	3.3	27.0	5.5	
Child Gender				0.04
Male	5.6	38.2	7.4	
Female	4.0	37.6	7.2	
Child Race/Ethnicity				< .001
Black	0.7	10.6	1.8	
Hispanic	1.4	20.4	4.9	
Other/ Multiple	1.7	9.8	2.5	
White	5.8	35.0	5.4	
Child First-Born Status				.10
No	5.7	46.0	8.1	
Yes	3.9	29.7	6.5	
Moved from birth state*				.26
No	8.4	67.5	12.8	
Yes	1.2	8.3	1.9	
Maternal Age (Years)				.03
≤ 29 years	3.0	29.5	5.4	
> 29 years	6.6	46.2	9.3	
Maternal Education				< .001
< 12 years (no HS degree)	0.8	12.1	2.2	
12 years (HS degree)	1.0	21.0	3.3	
> 12 years, no college degree	2.2	17.1	3.8	
College Graduate	5.6	25.6	5.4	
Income/Poverty Status				< .001
Above Poverty, > $75k	4.5	21.5	5.2	
Above Poverty, ≤ $75k	3.1	25.6	4.4	
Below Poverty	1.3	23.9	4.0	
Unknown	0.7	4.7	1.2	
Provider Type[i]				< .001
All Public	0.6	10.4	1.9	
All Hospitals	0.7	10.3	2.9	
All Private	6.8	42.5	6.9	
All Military/Other	1.0	1.0	0.8	
Mixed	0.5	11.6	2.2	

N= 14,751

*The only statistically significant difference when using a binary registry variable (p=0.06) versus a multi-level categorical variable (p < .001).

i- aggregated at child-level

model (results not shown) demonstrate minimal impact on the aORs with no changes in statistical significance when variables are added or subtracted in a stepwise manner.

Results from logistic regression. Results from regressing IIS participation on child up-to-date status controlling for child, maternal, and provider characteristics are shown in Table 3.3, except for individual state data that is excluded from the table due to the number of categories (See Appendix C).

There is no association between children whose providers submitted data to an IIS and child UTD vaccination status, however, children whose providers were unsure whether data was sent to an IIS are associated with lower odds of being UTD for the full combined series of vaccines (aOR 0.73, 95% CI 0.64, 0.83) when compared to children who had no providers reporting to an IIS. Provider type is associated with UTD status for some provider types. When compared with all public Providers, children who had all private, all military, or mixed provider types were associated with significantly higher odds of being UTD than those with all public providers (aORs= 1.29, 1.38, 1.27 respectively, 95% CIs 1.12-1.48, 1.02-1.85, 1.04-1.53) though the association is strongest for all private providers ($p < .001$).

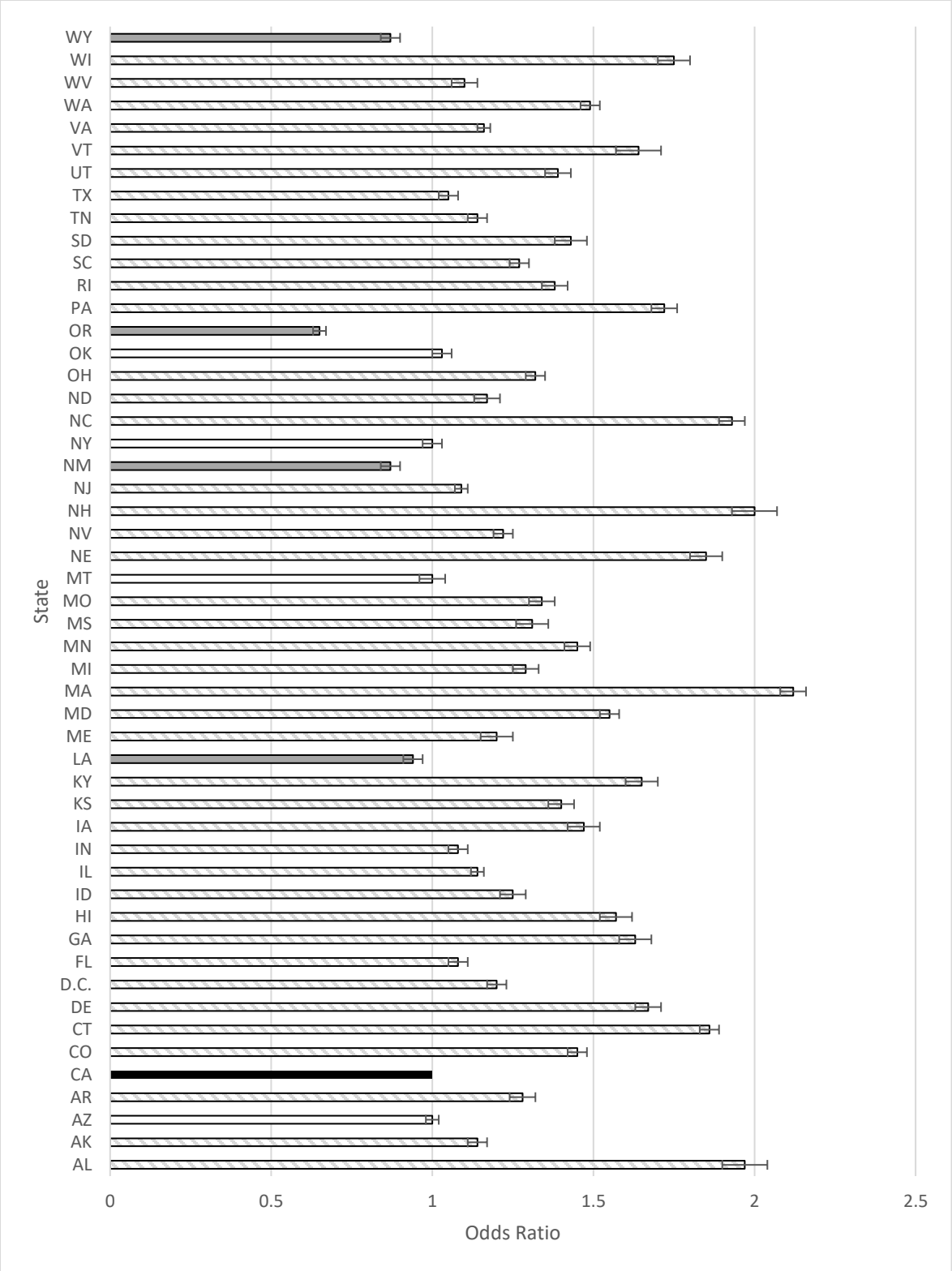
Where children live and whether that differs from where they were born are both associated with children's up-to-date status (Figure 3.3). Variation among state of residence ranges (See Appendix) from states associated with significantly lower odds (Oregon, aOR= 0.65, 95% CI 0.62, 0.69) of up-to-date children to those that are associated with significantly higher odds of being up-to-date (Massachusetts, aOR= 2.12, 95% CI 2.04, 2.20) when compared to California. Forty-five states and D.C. are associated with UTD status when compared to the reference state, with 4 states (LA, NM, OR, and WY) associated with lower odds and the remaining 41 states and D.C. associated with higher odds of being UTD. Regional differences were only notable for states in the Western region; compared to states in the

Table 3.3 Adjusted Odds Ratios of IIS Participation on Up-to-Date status on Children 19-35 months in the NIS

Outcome: UTD Status	aOR	95% CI
IIS Participation		
None	Ref	
Some/ All	1.14	[1.00, 1.29]
Unknown/ Don't Know	0.73***	[0.64, 0.83]
Prov Fac Type		
All Public	Ref	
All Hospital	1.12	[0.95, 1.33]
All Private	1.29***	[1.12, 1.48]
All Military	1.38*	[1.02, 1.85]
Mixed	1.27*	[1.04, 1.53]
Moved from Birth State		
No	Ref	
Yes	0.53***	[0.46, 0.62]
Maternal Age		
≤ 29 years	0.85***	[0.78, 0.93]
> 29 years	Ref	
Maternal Education		
< 12 years (non-HS grad)	0.69***	[0.58, 0.83]
12 years (HS grad)	0.72***	[0.62, 0.83]
> 12 years, Non-Coll Grad	0.79***	[0.71, 0.88]
College Grad	Ref	
Income/Poverty Status		
Above Poverty, > $75k	Ref	
Above Poverty, < $75k	0.74***	[0.66, 0.83]
Below Poverty	0.75***	[0.66, 0.84]
Unknown	0.80	[0.62, 1.02]
Child Age Group		
19-24 months	Ref	
25-29 months	1.48***	[1.35, 1.63]
30-35 months	1.48***	[1.34, 1.64]
Child Race/Ethnicity		
Black	0.86	[0.74, 1.00]
Hispanic	1.34***	[1.15, 1.56]
Other/Multiple	1.05	[0.93, 1.18]
White	Ref.	
Child Gender		
Male	Ref	
Female	1.00	[0.93, 1.08]
Child First-born Status		
No	Ref	
Yes	1.49***	[1.37, 1.63]
_constant	1.80***	[1.47, 2.21]
N= 14,751		0.045

* p < 0.05, ** p < 0.01, *** p < 0.001

Note: State is also in the model as a control (Ref: CA), results not shown due to space.



Legend: Black (Reference), White bars (no statistical significance), Gray bars (statistically significant, OR < 1.0), Shaded bars (statistically significant, OR > 1.0)

Figure 3.2 Adjusted Odds Ratios from Logistic Regression of States on UTD Status

Northeast region, states in the Western region have lower odds of being UTD (aOR = 0.76, 95% CI 0.61, 0.95- data not shown). Further, children who reside in a state different from where they are born have significantly lower odds of being UTD compared to those who remain in their birth state (aOR=0.53, 95% CI 0.46, 0.62).

Maternal factors (age, education, and income) are all highly correlated with children's UTD status. Younger maternal age (≤ 29 years) is associated with lower odds of having a child who is UTD compared to mothers > 29 years (aOR 0.85, 95% CI 0.78, 0.93). Similar trends are seen for maternal education. Mothers with less than high school, high school degrees but no college, and some college but no degree were all associated with lower odds of UTD status when compared to mothers with college degrees, however, odds do increase with levels of education (aOR 0.69, 95% CI 0.58, 0.83; aOR 0.72, 95% CI 0.62, 0.83; aOR 0.79, 95% CI 0.71, 0.88 respectively). Mothers whose household income is above $75k have higher odds of having UTD children than those below poverty (aOR 0.74, 95% CI 0.66, 0.84), as well as those above poverty but below $75k (aOR 0.75, 95% CI 0.66, 0.83).

Some child-level characteristics are also associated with UTD status. Odds of being UTD increases in older children. Compared to children 19-24 months, children 25-29 months and 30-35 months were associated higher odds of being UTD (aOR 1.48, 95% CI 1.35, 1.64 and 1.48, 95% CI 1.34, 1.63 respectively). Child race/ethnicity is only associated with UTD status for one group. Hispanic children have significantly higher odds of being UTD (aOR= 1.34, 95% CI 1.15, 1.56) than White children. Lastly, birth order demonstrates a statistically significant relationship with UTD status. Children who are first-born children have higher odds of being UTD than those of higher birth order (aOR= 1.49, 95% CI 1.37, 1.63).

Discussion

Freeman and Defriese stated that one of the intentions of registries was to increase immunization rates in the U.S. (Freeman & DeFriese, 2003). Measuring the effects of the investments in IIS, using data directly from the IIS, is still in early stages as many of the state and local IISs are still validating their data and experiencing complications with data quality (Khare, Piccinino, Barker, & Linkins, 2006; Robison, 2015). The NIS is the largest, most established, data source that publicly provides information on vaccines and IIS participation. This study contributes to the literature in several ways. First, it provides an updated analysis on the relationship between providers who have submitted data to an IIS and the odds of a child being up-to-date on routine vaccines. Two studies examined IIS participation on UTD in various ways, but the studies are more than a decade old (Kim et al., 2007; Mennito & Darden, 2010). Logically, states with IISs in those studies (exact number not available) are more mature and in theory would be expected to show larger impacts on vaccination rates over time. Similar to previous studies that reported on this relationship with NIS data from 2004-2006, I find no association between IIS participation and increased rates of UTD vaccination (Kim et al., 2007; Mennito & Darden, 2010). Consistent with the study by Kim et. al., children's providers who are unsure whether vaccines were submitted to an IIS have lower odds of completing the full combined series of vaccines compared with children whose do not have providers that participate in IISs. This finding suggests a persistent knowledge gap (Kim et al., 2007) or that providers' awareness of IISs, or other immunization policies and programs, may be associated with child vaccination status.

Second, I find that state of residence and geographic mobility is significantly correlated with UTD status for this sample. Although state immunization rates can be found in the

literature, few studies have included it as a significant contributor to the discussion on immunization rates (Hill et al., 2015; Luman, Barker, McCauley, & Drews-Botsch, 2005) as most discussions focus on national-level estimates or in small targeted locations. I find that UTD status for children ages 19-35 months varies significantly across the states after accounting for potential effects of State policies by clustering the error terms. The range of results (aOR: 0.65 (Oregon) to 2.12 (Massachusetts)) suggest that states may have a significant influence on child vaccination status and is further explored in Chapter 5 of this dissertation.

Additionally, mobility appears to be an important indicator of childhood vaccination status. Children who resided in a state different from their birth state are significantly less likely to be up-to-date which may increase the risk for medical record fragmentation by increasing the overall number of vaccine providers (Hamlin, Wood, Pereyra, & Grabowsky, 1996). Children who moved out of state were also less likely to have all their providers respond to the survey according to the findings in this study. Transferring care to another provider can create challenges in care continuity and it is possible that not every immunization provider was identified during the household interview phase of the NIS and thus were left out of the provider record check phase of the survey or that providers may be uncertain about their role in the NIS if their patient is new or perhaps no longer under their care. The magnitude of this finding was surprising and supports the need for IIS linkage or a national IIS that providers can access in real-time.

Third, this study also adds to the overall discussion of childhood vaccination rates. Child, maternal, and provider factors are all known contributing factors in whether children receive their recommended vaccines (Luman et al., 2003; Sturm, Mays, & Zimet, 2005). In studies reporting findings using NIS data, child age group is not frequently discussed as a significant

predictor of immunization rates (Hill et al., 2015; Stokley, Maurice, Smith, & Klevens, 2004). In this study, children in the older two age groups are associated with higher odds of receiving the full combined series of vaccines when compared with those less than 24 months old. This may be explained by vaccination policy variations by child-care providers. According to the U.S. Census Bureau, younger children are more likely to have child-care arrangements with relatives or non-center-based environments, and as they age, may be more likely to be enrolled in center-based day cares and pre-schools like Head Start (Laughlin, 2013). Center-based organizations typically have vaccination policies similar to those of schools which have been associated with increases in vaccination rates (Diekema, 2014; Freeman & DeFriese, 2003).

My findings are also inconsistent with the literature on immunization disparities by child race/ethnicity. Hill et. al. reports on this racial disparity in the NIS frequently through the MMWRs published by the CDC. The authors find that black children have lower rates of vaccination compared with white children (Hill et al., 2017; Hill et al., 2015). I find no difference in the UTD status for black children or children with multiple/other race ethnicities compared to white children in this study. However, I do find that when adjusting for maternal factors, location, and IIS participation, Hispanic children are associated with significantly higher odds of UTD vaccination, a finding that differs from other studies (Hill et al., 2015; Kim et al., 2007). These differences may be methodological as I control for states of residence, mobility, birth order, and record of a Hep B birth dose; when state is removed from my model, I find a shift in the effect to be more in alignment with previous studies- statistically lower odds in black children and no effect for children of Hispanic ethnicity.

First-born status' positive correlation with UTD status is a significant finding in this study. Birth order, while occasionally mentioned in the vaccine literature, is not frequently

discussed. I find that children who were first-born have significantly higher odds of being fully vaccinated than those who were not first-born. In one case, it is plausible that mothers with multiple children would have increased awareness, knowledge, and exposure to vaccinations leading to more informed decision-making. However, it has been demonstrated that lower birth order is correlated with higher vaccination rates (Dombkowski, Lantz, & Freed, 2004; Schaffer & Szilagyi, 1995). This may be due to the challenges with coordinating preventive care services for multiple children, who may have different vaccination requirements, since the schedules change by age, and the perceived barriers by larger families trying to stay compliant (Sabnis & Conway, 2015). This finding suggests that additional support may be needed for larger families to ensure timely vaccines for all children.

Results in this study also show that the odds of a child being up to date on their vaccinations varies by maternal characteristics. These data are largely consistent with the literature and suggest that higher incomes and increased education are associated with higher likelihood of vaccine uptake (Hill et al., 2015). Additionally, the literature suggests mothers will choose vaccination providers that align with their own beliefs on vaccination which may be correlated with age, education, exposure, and access to vaccines (Dombkowski et al., 2004; Luman et al., 2003; Mergler et al., 2013). In this study, I find that children with all private providers are correlated with higher odds of complete vaccination compared to children with all public providers, a finding consistent with a study by Luman et al. (2002), but inconsistent with a previous report of no effect by provider type (Kim et al., 2007). The parent-provider relationship regarding vaccination behaviors is particularly interesting and these findings could indicate a potential interaction between maternal behavior and provider characteristics.

Finally, my study contributes to the literature by providing a fuller model to examine the relationship between IIS participation and UTD status for the full combined vaccine series. According to the study by Freeman and colleagues, 30% of children in an under-vaccinated group had changed providers since birth which can increase the possibility of record fragmentation, poor continuity of care, and missed opportunities (Freeman & DeFriese, 2003). In this study, 10.7% of children with adequate provider data were no longer living in their birth state with a statistically higher proportion of mobile children lacking adequate provider data (p = .026). Mobility may also be associated with different socioeconomic status and parental behaviors since a long-distance move requires resources may not be available to vulnerable families. Geography can also play a key role in childhood immunizations; immunization programs are implemented and governed by the individual states in the U.S. I include state as a control but also use states' fixed-effects improve the specification of the model.

Limitations

There are several limitations in this study. First, the cross-sectional design of the NIS limits the ability to conclude a causal effect. Initially, I explored an instrumental variable approach because of anticipated endogeneity, but when tested, none of the variables were deemed endogenous nor was a good instrument discovered. Second, there were some differences in children whose providers returned the provider-check survey compared with those who did not, as well as differences in providers who submitted data to an IIS compared with those who did not. Questions in the provider record check such as whether data was sent to an IIS, are self-reported by providers and are not verified as to the existence of an IIS or directly validated with an IIS and are subject to reporting errors. Survey and provider weights were used at different points of analysis to try to account for differences among the groups in this study. Third, the

regression model did not explain a large portion of the variance in UTD status in this study and wide confidence intervals and a decrease in coefficient precision from clustering the error terms may have affected the statistical significance as it reduced the sample size to the number of clusters (N = 51). I decided on a conservative approach to not over-inflate the importance of the findings. I also anticipate that some of this explanation is lost in the recoding of the raw data for public-use or is not able to be captured through the NIS. Accessing the raw data through a Federal Research Data Center may improve the fit of the model, however, it is more likely that the NIS may not be sufficient as a stand-alone data source to answer this research question.

Finally, I made several assumptions to the data, based on my conceptual framework, by proxying for maternal beliefs and provider beliefs by including maternal characteristics and type of provider facility in the regression model. Prior to 2012, parental knowledge of childhood vaccines was collected in phase I of the NIS, however, those questions were removed to reduce the survey length. Adding questions in Phase I of the survey on parental beliefs toward vaccines may help improve the model. The NIS is not sufficient to explicitly study "providers" according to the NIS Data User Guide. Finally, while the NIS is the gold-standard for analyzing immunization data in the U.S., there are children outside of the sampling frame, such as those without landline or cell phone service, who would not be screened for inclusion in the NIS. The NIS uses a complex stratified survey design and complex survey weights to account for those children and to make the survey representative, but information on those children outside the sampling frame is not available and affects the generalizability of these results.

Conclusion

Expanding the utilization of Immunization Information Systems is one strategy recognized by public health officials and policymakers to improve vaccination rates by providing

vaccine recommendations in real-time while the child is in a provider's office and improving vaccine inventory tracking and ordering. Over the last twenty years, substantial investments have been dedicated to improving the infrastructure and utilization of Immunization Information Systems but there is scant literature regarding the impact of IISs on progress toward meeting the nation's immunization goals. Findings in this study suggest no relationship between child up-to-date status for the full combined series of vaccines and whether their providers submitted data to an IIS, though children whose providers were unsure of their IIS participation status were associated with lower odds of vaccine series completion. Several factors were identified as significant contributors to up-to-date status including state of residence, mobility, and first-born status suggesting a complicated dynamic between child, maternal, provider, and state immunization programs. A deeper examination into how these factors are associated with immunization rates would help public health officials understand these relationships and lead to potential new interventions to improve immunization rates.

Chapter 4 The Association Between Immunization Information Systems and Invalid Doses in Children 19-35 months of Age in the National Immunization Survey

Introduction

Relatively high and sustained rates of vaccination have resulted in reductions as much as a 99.9% in vaccine-preventable diseases in the U.S. (Chen, 1999; Roush & Murphy, 2007). However, waning immunity and decreases in vaccination rates threaten the progress of vaccination efforts. For example, recent studies have shown that immunity to the current child formulation of the Diphtheria Tetanus and aceullar Pertussis (DTaP) vaccine begins to wane as early as five years after administration of the fifth dose (Klein, Bartlett, Rowhani-Rahbar, Fireman, & Baxter, 2012; McGirr & Fisman, 2015), yet current vaccines schedules approved by the Advisory Committee on Immunization Practices (ACIP) do not include recommendations for additional boosters for most people; an additional dose is recommended once during teenage years, during each pregnancy, in adults with no or uncertain history of pertussis vaccination and in people over 65 who are expected to have close contacts with infants and children (Centers for Disease Control and Prevention, 2011). Additionally, the protective effect of the vaccine, measured as a titer, or the level of antibodies in circulation, following the Measles, Mumps, and Rubella (MMR) vaccine has also demonstrably decreased over time resulting in vulnerability to the highly contagious infections (Davidkin, Jokinen, Kontio, Paunio, & Peltola, 2012; LeBaron et al., 2007).

In addition to waning immunity, rates of vaccination have declined for several vaccines when compared to previous years and is correlated with increases in vaccine hesitancy and decreasing confidence in vaccines (Hill et al., 2017; Salmon, Dudley, Glanz, & Omer, 2015). In 2016, 70.7% of children 19-35 months of age were up-to-date (UTD) for the full series of recommended vaccines including ≥ 4 DTaP doses, ≥ 3 Polio doses, ≥ 1 Measles Mumps and Rubella dose, ≥ 3 Haemophilus influenzae b doses, ≥ 3 Hepatitis B doses, ≥ 1 Varicella dose, and

≥ 4 Pneumococcal doses. That UTD rate is down 1.5% points compared to 2015 and is the lowest since 2013 (Hill et al., 2017). These rates also demonstrate a failure of the U.S. to meet one of the Healthy People 2020 immunization objectives of 80% vaccination for the full series by the age of three years (US Department of Health and Human Services, 2011b). As a result, the population's protection toward vaccine-preventable diseases is reduced and outbreaks in vaccine-preventable illness are on the rise (Cherry, 2012; Phadke, Bednarczyk, Salmon, & Omer, 2016; Salmon et al., 2015). Along with increases in morbidity and mortality, these outbreaks are associated with increased costs and utilization of health care system resources (e.g. physician visits, hospitalizations) (Ortega-Sanchez, Vijayaraghavan, Barskey, & Wallace, 2014).

The ACIP approves the child and adult recommended vaccine schedules, including both the recommended ages and intervals between doses for each vaccine, which are based on "age-specific risks for disease, age-specific risks for complications, age-specific responses to vaccination, and potential interference with the immune response by passively transferred maternal antibodies" (Centers for Disease Control & Prevention, 2019). The ACIP also publishes the minimum ages and intervals required between doses in a series based on vaccine safety data which vary from the ACIP recommended schedules (Ahmed et al., 2011; Hamborsky, Kroger, Wolfe, Control, & Prevention, 2015). Children who receive a dose before the dose-required age have a higher likelihood of having a reduced or absent immunological response to the vaccine and leaves them susceptible to disease (Hamlin et al., 1996); they may also have higher risks of adverse reactions as the vaccines have not been tested for safety and efficacy at those ages (Luman et al., 2002). Further, doses that are administered too close to each other may not stimulate robust immune responses (Butte et al., 2001; Jilg, Schmidt, & Deinhardt, 1989) and

may limit the overall protective effect of those doses even though they will appear to be vaccinated against disease.

Vaccinating children outside of the validated ages and intervals, and failure to receive a full series, may give the impression of a vaccinated and protected population, when, the protective benefits of individual and herd immunity are not optimal and may leave the population vulnerable to infection. For example, receiving vaccines too early in age can interfere with the immune response. When administered before one year of age, the presence of maternal antibodies transferred during childbirth in a child's circulation may prevent them from developing their own antibodies to the measles, mumps, and rubella (MMR) vaccine (Ceyhan, Kanra, Erdem, & Kanra, 2001). While the child would have an MMR recorded and appear vaccinated in their health record, their lack of response to the vaccine would not offer full protection against measles.

This effect is also demonstrated in larger populations such as in the 1990 Pennsylvania measles outbreak. Of the more than 27,600 cases of measles reported during the outbreak, only 5,100 (18.4%) were appropriately vaccinated, and 22,500 (81.4%) were unvaccinated, which includes children who may have received untimely or inappropriate vaccinations (Centers for Disease Control, 1991). Of those children who were categorized as unvaccinated, 12,268 (44.3%) were inappropriately vaccinated and received their measles vaccine before the age of one year and demonstrates the importance of the timing of vaccines in addition to receiving the correct number of doses. These children did not have the benefit of optimal individual protection and because there were so many, likely lowered the protective herd immunity benefits.

Doses that have been administered too young or too close together are deemed "invalid" and require re-vaccination at the appropriate age and/or interval for optimal protection against

VPDs (Centers for Disease Control & Prevention, 2019). Re-vaccination adds to the number of clinic visits, increased costs and utilization of vaccine resources, and represents unnecessary exposure to biological substances (Stokley et al., 2004). These additional vaccinations may also increase the risk potential for adverse reactions. The full impact of invalid doses is unclear in the current immunization estimates since all doses given to a child are included in vaccine estimates regardless of whether they meet the required or recommended age and intervals for administration (Luman et al., 2005). One study from 2000 examined the number of invalid doses, and the cost of re-vaccinating children who had received them, and determined that at least 11% of children ages 19-35 months had one or more invalid vaccine doses when using the most stringent ACIP criteria (Stokley et al., 2004). The authors' cost analysis estimated a vaccine purchase cost of $10M to $18M for re-vaccinating these children which demonstrates added cost and burden of inappropriately timed vaccines.

Reducing invalid vaccines, and therefore increasing the overall quality of vaccine delivery, is a complex problem. The delivery of vaccines is complicated by increasing numbers of vaccine providers which causes fragmentation of immunization records (e.g. when a child sees a new provider or moves out of state and fails to migrate their records) (Hamlin et al., 1996; Stokley et al., 2001; Yusuf et al., 2002). Increasingly complex immunization schedules (Butte et al., 2001) may add additional complications for providers and parents trying to track immunizations. Parental and provider vaccine hesitancy regarding the safety and efficacy of vaccines also contributes to non-compliance to the recommended vaccine schedule and missed vaccination targets. As a result of vaccine hesitancy, parental and clinician mistrust of vaccines, vaccine manufacturers, and other vaccine advocates, (Larson et al., 2014; Mills, Jadad, Ross, & Wilson, 2005), many parents are opting to use alternative vaccination schedules (Feemster &

Offit, 2013; Offit & Moser, 2009) which further increases the opportunity for missed and under-vaccinated children.

One suggested strategy to improve the quality of vaccinations administered, and reduce the number of invalid vaccines, is through the utilization of immunization information systems (Freeman & DeFriese, 2003; Stokley et al., 2004). These population-based electronic repositories offer a centralized hub for not only storing immunization data, but sharing data with other providers and/or states and forecasting future immunization needs in real-time (Groom et al., 2015) so providers can administer the right vaccine to the right patient at the right time- a central tenet to patient-centeredness. These coordinated efforts are anticipated to reduce scattering and fragmentation of records, missed opportunities, and inappropriately delivered vaccines (National Vaccine Advisory Committee, 1999; Stokley et al., 2001; Yusuf et al., 2002).

Currently, there is no national immunization data tracking system (Gostin & Lazzarini, 1995). In the U.S., the first IIS was established in 1974 (Ortega et al., 1997). After several philanthropic efforts to expand their utilization stalled, the Clinton administration's immunization initiative allowed for federal dollars to be invested for the expansion and utilization of IIS at the state and local levels (Freeman & DeFriese, 2003). Although there have been substantial changes in IISs over the last ten years, and every state now operates at least one IIS either at a state, regional, or local level, there has been little research on the effects these IIS are having on vaccination rates and/or the quality of vaccine delivery (Kempe et al., 2001). Using the National Immunization Survey (NIS), the current gold-standard for immunization data in the U.S., I examine the relationship between IIS utilization and invalid vaccinations in children 19-35 months of age. In this paper, I address the following questions: First, how have invalid doses for the full recommended series changed from 2012 to 2016; and second, are

children whose providers submitted immunization data to an IIS less likely to have an invalid dose?

Conceptual Framework

Vaccination policies occur at the national and state-levels in the U.S. In order to achieve immunization goals, vaccine uptake strategies are enacted through a series of complex and dynamic relationships between public health entities, providers, and parents. Using the Conceptual Framework from Chapter 3 (Figure 4.1), I analyze the effect of IIS participation on invalid doses. Using my conceptual framework and the ACIP's criteria for minimum required age and interval between doses, I determine the validity of each dose in the most recent five years of National Immunization Survey Data. In my models, I include child characteristics as controls, as well as maternal characteristics since a child's mother is often the most influential person in vaccine decision-making (Luman et al., 2003). I include characteristics that are potential influencers of the mother's knowledge and behavior since this cannot be directly measured by this dataset, such as whether a child received a birth dose of the Hepatitis B vaccine. Finally, provider characteristics are included in the model as covariates to determine if certain provider types are associated with the quality of vaccines (e.g. invalid doses) and as my predictor of interest, I include a variable that proxies for provider participation in an IIS.

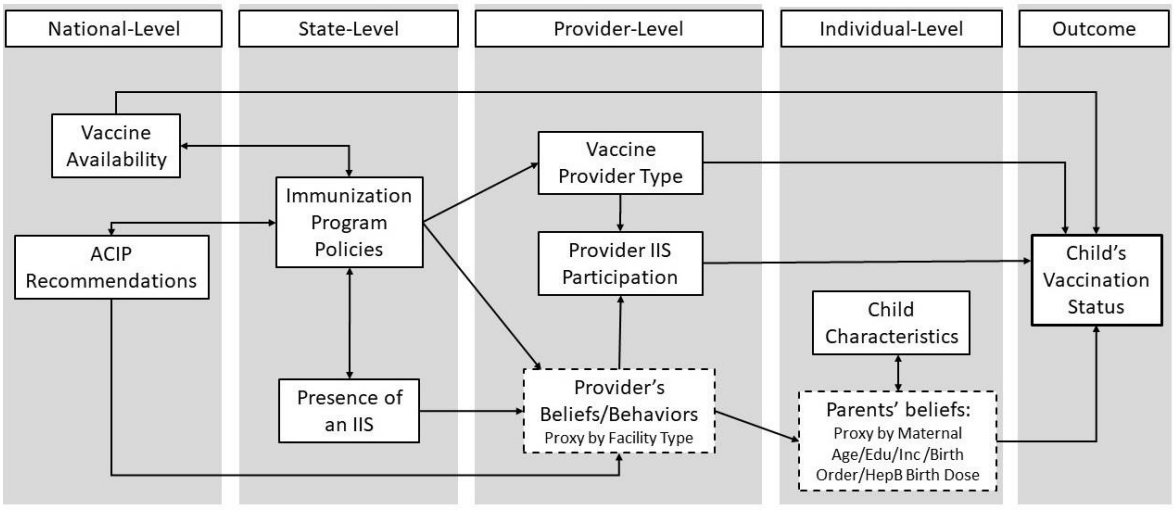


Figure 4.1 Conceptual Framework for Child Vaccination Status as presented in Ch. 3 (Fig 3.1)

Methods

This study is a retrospective secondary analysis of an annually conducted, nationally representative, cross- survey of households with children ages 19-35 months of age and their immunization providers from 2012 to 2016.

Data source. Five years of data from the 2012-2016 National Immunization Surveys (NIS) are included in this study. The NIS is conducted via a two-phase process summarized here but described in detail elsewhere (Smith et al., 2001; Zell et al., 2000). The first phase screens for households with children in the targeted age range of 19-35 months. Household screening is conducted using random-digit dialing (RDD) and a dual frame design that encompasses sampling techniques for both telephone landlines and mobile numbers. During this first phase, demographic, household, and vaccine provider information is collected from the person in the household with the most knowledge about the eligible child's vaccines- typically a parent or guardian (National Center for Immunization and Respiratory Diseases, 2017). Additionally, the

parent/guardian is asked for consent to contact the child's vaccination providers to obtain their immunization records.

The Provider Record Check is the second phase of the NIS where a survey is mailed to all providers for the eligible child(ren) who were identified in phase I. Providers are asked to list all vaccines in a child's record (including historical vaccines), vaccine type/manufacturer, dates administered, and if the provider reporting the vaccine is the one who administered the doses. Additionally, a question pertaining to whether the child's vaccines were reported to a registry is included in the survey.

Study sample. Children aged 19 to 35 months during the survey periods in the 2012 to 2016 NIS, with adequate provider data, and residing in the fifty states and Washington, D.C. are included in this analysis. Children living in Puerto Rico and other territories were excluded from this analysis since information about how IISs operate was inconsistent and/or incomplete at the time of this study.

The pooled 2012-2016 NIS data set includes 75,346 with adequate provider immunization data. Children who have received zero doses are also considered to have adequate provider data if a provider was identified by the parents and the provider responded with "child has received no vaccines". However, since this study examines the validity of vaccines, I exclude children with zero vaccines in the data set (N = 980) for a final sample size of 74,366.

Determination of vaccine dose validity. All doses in the recommended full series for children aged 19-35 months are evaluated for validity. The full series includes 4 DTaP, 3 Polio, 1 MMR, 3 Hib, 3 HepB, 1 Var, and 4 PCV doses (Hill et al., 2015). No changes were noted in the vaccine schedules and recommendations over the five-year study period.

Doses (e.g. DTaP 1, DTaP2, etc.) are evaluated using strict interpretations of the recommendations and flagged as “invalid” if they failed to meet the minimum required ACIP criteria for age and/or interval between doses. Doses that were administered before the minimum age criteria are “invalid due to age” whereas doses that were delivered too soon are considered “invalid due to interval”.

In many cases, children had received more than the recommended number of doses for a given series, for example, five polio doses when three are recommended. In these cases, the criteria for the “last” dose in the series is used to evaluate these doses for validity (e.g. a fifth DTaP dose was evaluated using the criteria for dose 4, or interval 4). There is no upper limit to the age and/or interval for classifying a dose as valid. The flags are created based on the specified ages and intervals as depicted in Figure 4.2 below.

Flags are created as binary variables for each possible dose and interval and indicated that the dose is valid (flag=0) or invalid (flag=1). Validity of the birth dose of Hep B is not determined since there is no minimum age, however, the interval between the birth dose and second dose of Hep B is evaluated.

Additionally, for retrospective analyses of immunization records, the Centers for Disease Control & Prevention recommends a 4-day grace period in most vaccine situations,

Figure 4.2 Minimum Required Ages and Intervals for Doses in the Full Combined Series According to ACIP Guidelines

except where noted (Centers for Disease Control & Prevention, 2015a). The ACIP recommends applying this grace period when determining vaccine dose validity to account for errors in entry or when providers miss a "vaccination window" due to weekends and/or holidays. This allowance also helps to provide conservative estimates in those children who might be receiving doses "close" to the required timing.

One challenge of retrospective analyses of NIS data is that the ACIP provides recommendations in weeks (up to 4 months) and in months thereafter, while the NIS captures ages of doses in days and months. I convert the ACIP recommendations into days by multiplying the number of weeks by 7 days or months by 30 days. The purpose of using days for the ages is to make it easier to apply the four-day grace period for retrospective analysis. This may introduce potential error into the dataset due to the different numbers of days per month. This method of determining age and validity has been used previously by Stokley et. al. (2004), but

was modified slightly to reflect the four day grace period and include the full recommended series.

Dependent variables. Three dependent variables are created for invalid doses: 1) any invalid, 2) invalid due to age, and 3) invalid due to interval. Each variable is first created as a dichotomous variable based on a series of flags created from the ACIP age and interval table described previously in Figure 2. First, a dose-level flag was created, followed by a vaccine-level flag, and then a full-series flag for each of the three dependent categories with "any invalid" combining both age and interval flags. However, since it is possible that one vaccine dose could be invalid for both age and interval, invalid doses were not additive. Figure 3 below demonstrates this multi-level flagging.

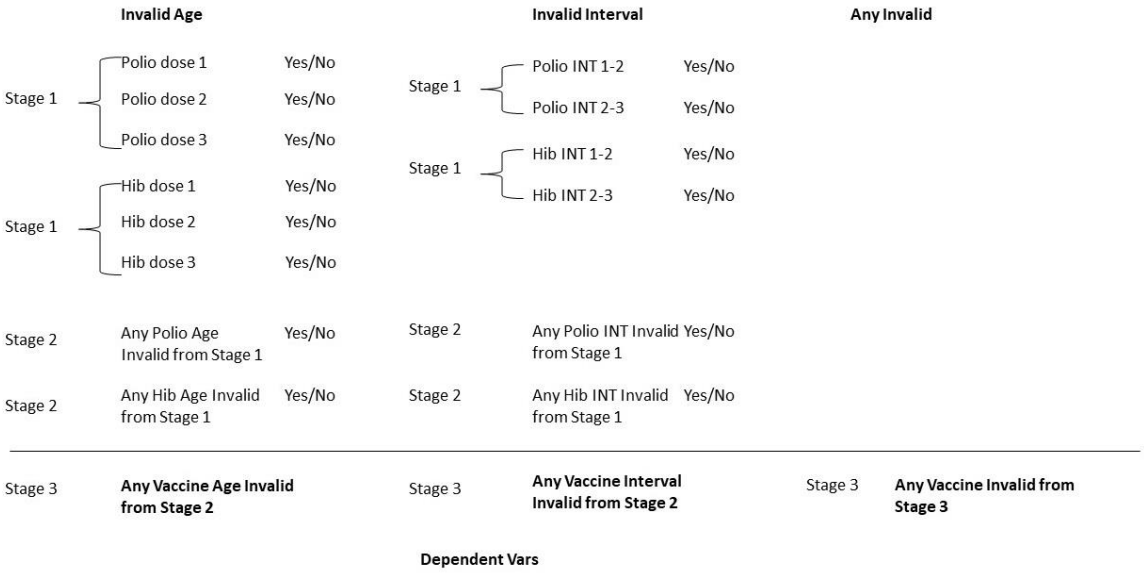


Figure 4.3 Diagram of Multi-level Flag Creation for Invalid Doses

Independent variables. The independent variable of interest is whether a child's data was submitted to a registry, hereafter called IISs. This data is collected in response to a question

on the provider record check survey in phase II of the NIS and is proxying for provider participation in an IIS. This categorical variable was initially provided in the data set as "no providers" submitted data to a registry, "some but probably or definitely not all" providers, "all providers", and those who marked "Unknown/Don't know". Because of the uncertainty around "some but probably or definitely not all", I recode the registry variable to reflect no participation, any participation, and unknown participation. I assume that those providers who are unsure of their registry participation may be different from those who opted to leave the survey question blank, and thus left them as a separate category.

The following independent variables are also included in the previous chapter of this dissertation.

Provider characteristics. This dataset does not capture much information about the provider, however, the type of provider(s) a child has (e.g. All public, All private, All hospital) is included and is used to proxy for provider's beliefs since providers choose their type of practice which is potentially influenced by their beliefs. For example, public providers are more likely to participate in federal vaccine funding programs and may be more likely to administer immunizations than private providers (Mennito & Darden, 2010). In the provider-record check portion of the survey, providers self-identify the type of facility they practice in (Centers for Disease Control and Prevention, 2016). Providers may select multiple choices from the facility type including private (solo, group, or health maintenance organization), hospital-based clinic, public health clinic, military hospital, various health centers (migrant, rural, community), and other facilities such as pharmacies, Women, Infants, and Children, and school-based clinics. I make the assumption that all public-health clinics, including rural and community health centers, are categorized as public facilities, hospital-based clinics as hospital facilities. Those that do not

fit into the criteria of public, private, or hospital, (e.g. pharmacies) are assumed to be categorized in the Military/Other category. The provider type variable is re-coded and aggregated at the child level in the public-use data file and prevents analyses of individual providers.

State-level influence. Current state of residence is included to help control for state-level immunization policies. There are currently no national laws, however, the ACIP makes national recommendations which are then carried out by state immunization programs. These immunization policies also affect state-run IISs and may influence provider behavior. Policies and behavior at within a state may change over time, so I also control for year fixed effects and an interaction between year and state. Additionally, I include a variable that assesses mobility (Yes/No) measured by whether a child lives in a different state from where they were born to adjust for state selection effects of vaccination history.

Maternal characteristics. Previous literature on vaccination behaviors suggests that mothers are the most influential person in childhood vaccination decisions (Luman et al., 2003); their attitudes toward vaccination were significantly predictive of infant vaccination status (Fadel et al., 2017). There is no direct way to measure maternal beliefs and behavior, so I proxied for it in several ways. I select variables that have been identified in the literature as influential on a mother's vaccine knowledge and decision-making (Luman et al., 2003) including: maternal age, maternal education, a household income and poverty variable, and whether a child received a birth dose of Hep B vaccine.

Younger maternal age has been associated with lower child vaccination rates (Luman et al., 2003), so controlling for maternal age (≤ 29 yrs or > 29 yrs) is important when evaluating the effect of IIS on rates. The effect of maternal education is less clear on child vaccination status. For example, older studies have shown that advanced maternal education is associated with

higher rates of childhood vaccinations (Luman et al., 2003), however, more recent studies have shown there are clusters of individuals with graduate or professional school education who are less accepting of vaccines (Healy & Pickering, 2011). Therefore, I include maternal education (< 12yrs, 12 yrs, > 12 yrs- non-college grad, College Grad) as a control to help improve the fit of the model.

Disparities in vaccination rates have also been identified based on socio-economic status (Reich, 2014), therefore, I include a poverty status variable, available for all children, that is based on the 2011 through 2015 Census data for poverty thresholds (Centers for Disease Control & Prevention, 2017). This variable is coded as "below poverty", "above poverty but less than $75k" and "above poverty and more than $75k" and an "unknown/refused to answer" group. Poverty thresholds are determined annually using the using data from the Census Bureau (National Center for Immunization and Respiratory Diseases, 2017). I control for year fixed effects in my models to adjust for the annual change. Finally, the birth dose of Hep B may proxy for maternal beliefs and behaviors towards vaccination and has been used elsewhere in the literature as a covariate or control (Mennito & Darden, 2010; Yusuf et al., 2000). Accepting the birth dose of Hep B might provide insight to the maternal beliefs about vaccination at a critical time in parent and child-development.

Child characteristics. Child characteristics are included in the model as controls. The ACIP recommendations for the full series of routine vaccination, excluding the annual vaccines for Flu prevention and the Rotavirus series, to be completed by 18 months of age, therefore, this sample of 19-35 months of age old children should all have completed the series at the time of data collection (Zell et al., 2000). I use child age group in months (19-23, 24-29, 30-35), gender (Male/Female) and race/ethnicity (Black, Hispanic, White, Multiple/Other) as controls. I include

the child's race/ethnicity as a control in the model since there are known disparities in the immunization rates for vulnerable populations which are typically racially diverse (Hill et al., 2015). Lastly, I include an indicator for first-born status (Yes/No) because children at lower birth orders are more likely to be UTD (Brenner et al., 2001).

Analysis. The analysis plan for this research question consists of a series of bivariate statistical tests and a set of regression models which are developed with guidance from the conceptual framework.

Bivariate statistics. First, to look for potential sources of selection bias, I conducted a series of corrected, weighted Pearson chi-square statistics or design-based F statistics to determine significance ($\alpha = .05$). I present the summary statistics using column percentages to compare the distribution of characteristics over the five-year study period using the provider survey weights in the public-use file as recommended by the data user guide (National Center for Immunization and Respiratory Diseases, 2017).

Next, in order to attribute any meaningful change to the predictor (IIS Participation), I test for statistically significant differences on the sample, aggregated across years, by provider IIS participation.

Invalid dose assessment. Invalid doses are analyzed at the child-level and presented as counts (number of children) and percent of children with at least one invalid dose due to age, interval, or combined age or interval. Children with zero recorded vaccines are excluded for this analysis. Each vaccine (e.g. DTaP, Hib, etc.) for each year had a different denominator because of excluding children with "zero DTaPs in 2012" resulted in a different number than those

children with "zero Hib in 2014", as an example. The numbers of children are counted and then divided by the new denominator to get the proportion of children with invalid doses.

Regression analysis. To address my research questions, I utilize a series of three logistic regression models and cluster the error terms at the state-level to account for policies and programs enacted at the state level. This approach allows the error terms to be correlated within each cluster (Cameron & Miller, 2015). The states' fixed-effects capture state-level factors, such as preferences or cost difference, that are stable over time. Including state effects means that the IIS effects are estimated within state and then averaged across states. Three separate models were used to examine the effect of IIS participation on valid doses. The full model for the regression analysis is shown below, with descriptions of the three models by dependent variables. All variables in the models are categorical with variables in bold represent categorical variables with more than two levels.

$$\underline{\text{Full Model}}: \text{InvalidVars}_i = \beta_0 + \beta_1 * \mathbf{IISParticipation_{i1}} + \beta_2 * \mathbf{Year_{i2}} + \beta_3 * \mathbf{State_{i3}} + \beta_4 * \mathbf{(Year_{i4}\ X\ State_{i4})} + \beta_5 * \mathbf{ProviderType_{i5}} + \beta_6 * \text{HepBBirthDose}_{i6} + \beta_7 * \text{MaternalAge}_{i7} + \beta_8 * \mathbf{MaternalEducation_{i8}} + \beta_9 * \mathbf{IncPov_{i9}} + \beta_{10} * \mathbf{ChildAge_{i10}} + \beta_{11} * \mathbf{ChildRace/Ethnicity_{i11}} + \beta_{12} * \text{Gender}_{i12} + \beta_{13} * \text{FirstBorn}_{i13} + \beta_{14} * \text{Mobility}_{i14}\ \varepsilon_i$$

where InvalidVars represents three different dependent variables for invalid doses including a variable for "any invalid dose" (Model 1), "any invalid dose due to age" (Model 2), and "any invalid dose due to interval" (Model 3) and β_0 represents the invalid dose status for children when all predictor variables are held at zero. Provider-level variables include IISParticipation as an indicator for provider participation in an IIS and ProviderType as the facility type(s) that the child's provider(s) are employed within. Maternal factors include the MaternalAge, MaternalEducation, and IncPov, a measure of income and poverty threshold, as well as a dummy variable for whether any of the child's providers reported a HepBBirthDose which proxies for

maternal attitudes and behaviors toward vaccination. Child factors included as controls are ChildAge group, ChildRace/Ethnicity, child gender, first-born status, and a Mobility variable to indicate if a child had moved from their birth state.

In addition to the provider, maternal, and child factors described in the Data section, the model includes state-by-year fixed effects. These indicators for state and year are meant to capture changes in state policies or economic conditions that affect immunizations (e.g. changes in funding for public health departments).

For each regression model, I report the adjusted odds ratios (aORs) and the McKelvey & Zavoina's R^2 which most closely approximates the R^2 achieved by Ordinary Least Squares' regression (Institute for Digital Research and Education (IDRE), n.d.).

Results

Summary statistics. There are 126,657 children ages 19-35 months in the 2012-2016 NIS datasets, of which 75,346 (59.5%) have adequate provider data for inclusion in this study. The sample is reduced further when children with zero recorded doses for the 7 vaccines are excluded (N = 980) for a final sample size of 74,366 for the five years of pooled data with yearly sample size shown in Table 1. IIS status was available for all children retained in the data set. There are no statistically significant differences in the proportion of children with zero vaccines over time (data not shown); less than 1% of children each year, with adequate provider data, have zero recorded doses ($p = .80$).

In Table 4.1, using provider survey weights, I present a summary of the variables by year to assess whether there are any differences in my variable composition over time. There are no statistically significant differences over time for child age group ($p = .99$), gender ($p > .99$),

Table 4.1 Weighted Summary Statistics for Children 19-35 Months of Age in the 2012-2016 National Immunization Surveys with Adequate Provider Data and 1+ Reported Vaccines

	Year						
	2012	**2013**	**2014**	**2015**	**2016**	**Total**	***p***
Child Age Group							
19-23	29.7%	30.0%	30.4%	30.2%	30.2%	30.1%	.99
24-29	33.8	34.0	33.7	33.6	34.0	33.8	
30-35	36.5	36.0	35.9	36.2	35.8	36.1	
Child Gender							
Male	51.2	51.2	51.1	51.2	51.3	51.2	> .99
Female	48.8	48.8	48.9	48.2	48.7	48.8	
Child Race/Ethnicity							
Black	13.6	12.7	13.6	12.5	13.1	13.1	.25
Hispanic	27.3	27.2	26.4	26.8	26.7	26.9	
Other/Multiple	11.9	12.2	13.4	12.4	14.0	12.8	
White	47.2	47.9	46.6	48.3	46.2	47.2	
Child First-born Status							
No	61.2	60.0	60.0	59.0	59.8	60.0	.38
Yes	38.8	40.0	40.0	41.0	40.2	40.0	
Hep B Birth Dose[†]							
< 1 Providers reported	24.1	21.8	23.2	23.6	24.1	23.4	.13
≥ 1 Provider(s) reported	75.9	78.2	76.8	76.4	75.9	76.6	
Moved from birth state							
No	91.3	90.2	89.9	89.8	88.6	90.0	.002
Yes	8.7	9.8	10.1	10.2	11.4	10.0	
Maternal Age							
≤ 29 years	44.7	44.6	42.4	40.7	37.9	42.1	< .001
> 29 years	55.3	55.4	57.6	59.3	62.1	57.9	
Maternal Education							
< 12 years	18.8	18.3	17.7	15.7	15.1	17.1	< .001
12 years (HS degree)	27.1	25.7	25.1	26.1	25.4	25.9	
> 12 years, no college	22.4	22.2	23.6	23.2	23.0	22.8	
College Graduate	30.7	33.8	33.6	35.1	36.5	34.2	
Income/Poverty Status							
Above, > $75k	25.2	27.4	27.1	29.3	31.2	28.0	< .001
Above, ≤ $75k	33.3	33.9	33.9	32.1	33.1	33.3	
Below	36.8	33.4	33.6	32.8	29.2	33.2	
Unknown	4.7	5.3	5.6	5.8	6.5	5.5	
Provider Type							
All Public	12.1	12.7	11.8	12.0	12.9	12.3	.008
All Hospitals	11.4	12.5	12.5	12.4	13.9	12.6	
All Private	58.2	56.7	55.6	57.5	56.2	56.8	
All Military/Other	2.1	2.4	3.1	2.1	2.7	2.5	
Mixed	16.2	15.7	17.0	16.0	14.3	15.8	
N	**16,480**	**13,450**	**14,730**	**14,973**	**14,733**	**74,366**	

[†] Hep B birth dose flags are recorded as "No providers marked Hep B birth dose given" or "At least one provider marked that a Hep B birth dose was given".

race/ethnicity (p = .25), first-born status (p = .38), and receipt of Hep B birth dose (p = .13). However, over time, children are more likely to be living a state different from where they were born (p = .002) suggesting increasing mobility in the country. For children with adequate provider data, maternal characteristics varies over time. Mothers of these children tend to be older (p < .001), more educated (p < .001) with an increase in the number of mothers with college degrees, and nominally more affluent (p < .001) with an increase in the number of families reporting household incomes greater than $75k. Finally, the proportion of provider types, which may be reflective of shifts in family dynamics and behaviors, is notable for a slight shift in the number of respondents seeking vaccinations from "all hospital" and "all public" compared to "all private" providers or "mixed" (p = .01).

In Table 4.2, I summarize the children in the dataset by whether their providers sent data to an IIS. There are no statistically significant differences in IIS participation by child age group (p = .78), gender (p = .14), or whether a child resided in a state different from their birth state (p = .10). Differences in IIS participation are demonstrated in all other variables: race/ethnicity, first-born status, receipt of a Hep B birth dose, maternal characteristics (age, education, poverty status), and provider type. For those with no IIS participation, 8.0% were Black, 20.1% Hispanic and 57.4% White compared to those with some/all IIS participation (14.1%, 27.8%, and 46.0% respectively, p < .001). Children whose providers reported unknown IIS participation were more likely to be first-born (43.4%) compared to those with no participation (40.0%), or some/all participation (39.7%, p < .001).

Maternal characteristics also demonstrated important differences. The maternal age is only available as dichotomous information, however, a statistically significant higher proportion of mothers whose children have zero records in an IIS is seen for the older age group when

Table 4.2 Weighted Descriptive Statistics by IIS Participation in Children 19-35 Months of Age, with Adequate Provider Data, in the 2012-2016 National Immunization Surveys

	No IIS Participation		Some/All IIS Participation		Unknown IIS Participation		
	%	Range	%	Range	%	Range	p
Child Age Group							
19-23	29.6	28.1 / 33.9	30.3	29.1 / 30.8	29.8	27.5 / 33.6	.78
24-29	34.4	30.8 / 37.0	33.8	32.8 / 35.3	33.0	28.8 / 35.6	
30-35	36.0	34.5 / 39.4	35.9	35.2 / 36.8	37.1	34.8 / 38.3	
Child Gender							
Male	53.1	50.3 / 58.1	50.9	50.5 / 51.4	51.1	50.6 / 51.1	.14
Female	46.9	41.9 / 49.7	49.1	48.6 / 49.5	48.9	47.9 / 49.4	
Child Race/Ethnicity							
Black	8.0	6.7 / 9.3	14.1	13.6 / 14.0	13.0	12.1 / 14.7	< .001
Hispanic	20.1	14.4 / 24.6	27.8	26.9 / 29.1	28.4	25.4 / 33.5	
Other/Multiple	14.5	13.2 / 17.5	12.1	10.5 / 13.0	14.7	11.5 / 17.2	
White	57.4	55.2 / 60.5	46.0	45.0 / 47.8	43.9	37.1 / 47.1	
Child First-born Status							
No	60.0	56.9 / 62.5	60.7	59.5 / 61.5	56.6	54.4 / 58.3	.001
Yes	40.0	37.5 / 43.1	39.3	38.5 / 40.5	43.4	41.7 / 45.6	
Hep B Birth Dose[†]							
< 1 Providers reported	27.4	22.6 / 29.9	22.1	20.4 / 22.9	25.6	23.0 / 26.9	< .001
≥ 1 Provider(s) reported	72.6	70.1 / 77.4	77.9	77.1 / 79.6	74.4	73.1 / 77.0	
Moved from birth state							
No	89.9	87.2 / 91.4	90.2	89.1 / 91.5	88.8	87.0 / 90.5	.10
Yes	10.1	8.6 / 12.8	9.8	8.5 / 10.7	11.2	9.5 / 13.0	
Maternal Age							
≤ 29 years	31.6	29.0 / 34.5	44.4	39.0 / 48.4	40.2	36.5 / 45.3	< .001
> 29 years	68.4	65.5 / 71.0	55.6	51.6 / 61.0	59.8	54.7 / 63.5	
Maternal Education							
< 12 years	10.2	8.3 / 13.4	18.6	15.9 / 22.4	16.4	13.9 / 19.1	< .001
12 years (HS degree)	17.7	10.6 / 22.5	27.8	27.1 / 28.9	23.8	21.5 / 25.5	
> 12 years, no college	21.3	18.7 / 23.5	23.1	22.5 / 23.7	23.1	21.2 / 25.7	
College Graduate	50.8	46.1 / 58.2	30.5	27.3 / 33.8	36.7	35.2 / 38.2	
Income/Poverty Status							
Above, > $75k	44.7	41.8 / 46.9	24.3	20.0 / 28.4	31.3	27.9 / 35.3	< .001
Above, ≤ $75k	32.0	31.0 / 33.0	33.5	32.1 / 34.3	32.8	29.7 / 36.7	
Below	19.3	14.0 / 23.1	36.3	31.6 / 41.2	30.5	27.0 / 33.4	
Unknown	4.0	3.0 / 6.7	5.9	5.2 / 6.3	5.4	2.8 / 8.1	
Provider Type							
All Public	5.7	4.7 / 7.2	13.8	13.1 / 15.3	10.6	7.8 / 12.7	< .001
All Hospitals	7.6	6.6 / 8.6	12.1	10.7 / 13.6	19.7	18.2 / 22.8	
All Private	75.5	71.1 / 78.0	54.3	52.8 / 56.1	51.8	47.4 / 55.6	
All Military/Other	5.9	4.9 / 10.3	1.4	0.9 / 2.1	4.8	3.5 / 6.8	
Mixed	5.3	4.9 / 5.8	18.4	15.4 / 19.6	13.1	11.1 / 14.7	
Unknown/Missing[‡]	0.0	-	0.0	-	0.0	-	

N= 75,346

[†] Hep B birth dose flags are recorded as "No providers marked Hep B birth dose given" or "At least one provider marked that a Hep B birth dose was given".

[‡]Ranges not available due to the low number of observations in the Unknown/Missing category. Responses were omitted in further analyses.

compared to those with some/all providers reporting immunizations to an IIS (68.4% vs 55.6, $p <$ .001). Mothers of children who are associated with non-IIS-participating providers also tend to be more educated and in higher income households. Of those with no IIS participation, 50.8% of mothers are college graduates compared to 30.5% of those with some/all IIS participation. While the proportion of mothers above the poverty line, but with household incomes less than $75k, did not change much by IIS participation, the proportion of mothers above the poverty line with income greater than $75k is 44.7% in the no IIS participation group but only 24.3% in IIS participation group. This difference is inversely proportional to the women below the poverty line (19.3% and 36.3 respectively, $p < .001$).

Finally, provider type is associated with IIS participation differences. Private providers comprise 75.5% of the no IIS Participation group compared to only 54.3% ($p < .001$) of the IIS Participation group. This difference among IIS Participation was distributed across All Public, All Hospitals, and Mixed provider types. These variables are included in the conceptual model as controls due to the many differences associated with IIS participation.

Status of invalid doses. Invalid dose trends vary widely over the five-year data period. Data in Table 4.3 shows the count and percentage of invalid doses for age, interval, and combined age and interval. Overall, the number of children with invalid doses in the full series due to age and interval increases from 2012 (44.2%) to 2016 (50.4%). The two vaccines largely responsible for this increase are the Hepatitis B vaccine (+16.1%) and the Polio vaccine which saw initial decreases but has been trending upward in the most recent 2016 sample (29.1% in 2012 to 14.8% in 2014 to 20.6% in 2016) mostly due to invalid age at administration. When examining Hep B by interval and age, most of this change in invalid doses is due to age (+16.0%) when compared to the change in invalid intervals (+2.2%); invalid polio doses follows

a similar trend with initial decreases in invalid age doses from 2012-2014 (-14.3%) to increasing rates from 2014-2016 (+4.7%) and an overall decrease from 2012 to 2016 (-0.6%).

For the other five vaccines, very few changes are seen over the five-year period. Invalid DTaPs decline over time (-0.6% from 2012-2016) with improvements in both invalid doses due to age (-0.6%) and intervals (-0.5%). The percent of children with invalid PCV, Hib, and VRC doses remain largely unchanged (0%, 0%, and -0.1% respectively) over the five-year study period, however, there may be the start of an increasing trend in invalid MMRs due to age (from 1.0% invalid in 2012 to 1.4% in 2016). Lastly, from the data in Table 3, it is apparent that majority of invalid doses are due to doses that are administered at an age less than the minimum required age criteria published by the ACIP.

Table 4.3 Frequency and Percentage of Children in the 2012-2016 National Immunization Surveys with Invalid Doses Using ACIP Minimum Required Ages and Intervals

	Any Invalid					Invalid Age					Invalid Interval				
Vaccine	2012	2013	2014	2015	2016	2012	2013	2014	2015	2016	2012	2013	2014	2015	2016
DTaP	473	338	364	376	332	498	373	387	414	360	378	265	299	306	264
	(2.9)	(2.5)	(2.5)	(2.5)	(2.3)	(3.1)	(2.8)	(2.7)	(2.8)	(2.5)	(2.3)	(2.0)	(2.1)	(2.1)	(1.8)
Hib	200	162	190	159	172	170	165	194	141	164	89	77	86	77	82
	(1.2)	(1.2)	(1.3)	(1.1)	(1.2)	(1.0)	(1.2)	(1.3)	(1.0)	(1.1)	(0.5)	(0.6)	(0.6)	(0.5)	(0.6)
PCV	232	169	201	179	197	200	129	172	139	163	102	82	102	98	107
	(1.4)	(1.3)	(1.4)	(1.2)	(1.4)	(1.2)	(1.0)	(1.2)	(0.9)	(1.1)	(0.6)	(0.6)	(0.7)	(0.7)	(0.7)
MMR[b]	133	88	150	154	167	151	86	171	177	194	1	6	6	5	3
	(0.9)	(0.7)	(1.1)	(1.1)	(1.2)	(1.0)	(0.7)	(1.2)	(1.3)	(1.4)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)
Pol	4696	2986	2140	2428	2971	4833	3069	2263	2556	3073	360	255	265	263	225
	(29.1)	(22.6)	(14.8)	(16.5)	(20.6)	(30.0)	(23.3)	(15.7)	(17.4)	(21.3)	(2.2)	(1.9)	(1.8)	(1.8)	(1.6)
VRC[b]	74	41	61	57	56	58	30	46	52	58	24	13	18	14	8
	(0.5)	(0.3)	(0.4)	(0.4)	(0.4)	(0.4)	(0.3)	(0.3)	(0.4)	(0.4)	(0.2)	(0.1)	(0.1)	(0.1)	(0.1)
HepB	2719	2347	3525	5115	4788	2548	2203	3349	4929	4618	560	431	687	875	821
	(16.9)	(17.8)	(24.3)	(34.6)	(33.0)	(15.8)	(16.7)	(23.1)	(33.3)	(31.8)	(3.5)	(3.3)	(4.7)	(5.9)	(5.7)
Full	7287	5316	5641	7200	7429	8458	6055	6582	8408	8630	1169	873	1183	1368	1271
Series	(44.2)	(39.5)	(38.3)	(48.1)	(50.4)	(51.3)	(45.0)	(44.7)	(56.2)	(58.6)	(7.1)	(6.5)	(8.0)	(9.1)	(8.6)

[†]Data presented as Number of Children (%)
[a] Children with zero doses reported are excluded from this analysis.
[b] Only 1 MMR and 1Varicella dose is recommended for this age group, however, all doses were evaluated for validity.

Logistic regression of IIS participation on invalid doses. Three regression models are employed to examine the relationship between IIS participation and invalid doses for the full

series: the probability of having any invalid dose, having any invalid dose due to age, and any invalid dose due to interval as seen in Table 4. After I determined Hepatitis B as the primary driver of invalid doses (see Table 4.3), I made the decision to exclude the Hep B doses from the main regression models (Table 4.4) and present them separately in Table 4.5 of the results section of this chapter so as not to bias my interpretation of the regression results.

Models (1) and (2) have the same sample size (N = 73,189) and differs from Model (3)'s sample size of N = 72,115 because intervals are calculated from the number of doses, and not every child have the same number of vaccines administered. For the three models tested, the MeKelvey & Zavoina R^2 values were similar and ranged from explaining 9.8% (Model 1) to 10.2% (Model 2) of the variance of the dependent variables. The regression results using two of the independent variables ("any invalid" and "invalid due to age") were almost identical, so I focus mainly on discussing invalid doses due to age or interval. Further, an interaction term between IIS participation and year which resulted in similar coefficients and no statistical significance (data not shown), so the interaction was excluded from the final model.

These data show that IIS participation is not a statistically significant predictor of invalid doses for the full series for all three models (Table 4.4). When compared to children who had no providers reporting vaccines to an IIS, some/all IIS participation is not associated with invalid doses.

State of residence provided some of the most interesting results from the regression models, using states' fixed-effects, suggesting that state immunization programs probably have a strong influence on immunization behaviors. In this study, California is used as the referent state because of its size, diversity, and research on immunization programs in the state. For the fifty states, and D.C., aORs varied widely (Mean aOR = 1.48). Children from Rhode Island are

Table 4.4 Adjusted Odds Ratios of Provider IIS Participation on Invalid Dose Status Excluding Hep B Doses

Logistic Reg. Models:	(1) Any Invalid		(2) Invalid Age		(3) Invalid Interval	
	aOR	95% CI	aOR	95% CI	aOR	95% CI
IIS Participation						
None	Ref.		Ref.		Ref.	
Some/All Providers	1.08	[0.93, 1.25]	1.08	[0.93, 1.26]	1.15	[1.00, 1.34]
Unknown	1.06	[0.91, 1.23]	1.06	[0.90, 1.23]	1.11	[0.95, 1.31]
Year						
2012	Ref.		Ref.		Ref.	
2013	0.91	[0.82, 1.02]	0.89	[0.80, 1.00]	1.37***	[1.34, 1.40]
2014	0.67***	[0.60, 0.74]	0.70***	[0.63, 0.78]	0.82***	[0.80, 0.84]
2015	0.49***	[0.42, 0.58]	0.52***	[0.44, 0.61]	1.18***	[1.15, 1.21]
2016	0.69***	[0.60, 0.80]	0.72***	[0.62, 0.83]	0.54***	[0.52, 0.57]
Provider Type						
All Public	Ref.		Ref.		Ref.	
All Hospital	1.21*	[1.04, 1.41]	1.21*	[1.04, 1.42]	0.95	[0.80, 1.22]
All Private	1.21*	[1.04, 1.40]	1.20*	[1.04, 1.40]	1.02	[0.90, 1.14]
All Military/Other	0.61***	[0.49, 0.75]	0.57***	[0.46, 0.71]	0.78	[0.61, 1.00]
Mixed	1.33***	[1.19, 1.50]	1.33***	[1.18, 1.49]	1.65***	[1.43, 1.91]
Moved from birth state (No)						
Yes	1.26***	[1.16, 1.38]	1.25***	[1.15, 1.37]	1.87***	[1.65, 2.12]
Hep B Birth Dose (None)						
≥ 1 Provider(s) reported	1.21***	[1.13, 1.29]	1.22***	[1.13, 1.30]	0.74***	[0.67, 0.81]
Maternal Age						
≤ 29 years	0.98	[0.94, 1.02]	0.98	[0.94, 1.03]	1.13**	[1.04, 1.23]
> 29 years	Ref.		Ref.		Ref.	
Maternal Education						
< 12 years	0.88**	[0.80, 0.96]	0.87**	[0.79, 0.95]	1.10	[0.93, 1.31]
12 years (HS degree)	0.90***	[0.85, 0.96]	0.89***	[0.84, 0.95]	1.06	[0.94, 1.21]
> 12 years, non-college grad	0.89***	[0.85, 0.93]	0.89***	[0.85, 0.93]	0.93	[0.83, 1.03]
College grad	Ref.		Ref.		Ref.	
Income/Poverty Status						
Above Poverty, > $75k	Ref.		Ref.		Ref.	
Above Poverty, ≤ $75k	0.95	[0.90, 1.00]	0.95	[0.91, 1.00]	1.19**	[1.08, 1.32]
Below Poverty	0.94	[0.88, 1.01]	0.94	[0.87, 1.00]	1.38***	[1.21, 1.58]
Unknown	1.01	[0.91, 1.12]	1.01	[0.91, 1.11]	1.48***	[1.19, 1.82]
Child Age Group						
19-24 months	Ref.		Ref.		Ref.	
25-29 months	1.18***	[1.12, 1.25]	1.18***	[1.11, 1.25]	1.15**	[1.06, 1.25]
30-35 months	1.25***	[1.19, 1.32]	1.25***	[1.19, 1.32]	1.17**	[1.06, 1.29]
Child Race/Ethnicity						
White	Ref.		Ref.		Ref.	
Black	0.90**	[0.84, 0.97]	0.90**	[0.83, 0.97]	1.41***	[1.20, 1.66]
Hispanic	0.99	[0.93, 1.06]	0.98	[0.91, 1.05]	1.25***	[1.10, 1.43]
Multiple/Other	1.12**	[1.04, 1.22]	1.12**	[1.03, 1.21]	1.58***	[1.39, 1.79]
Child Gender (Male)						
Female	1.00	[0.96, 1.03]	1.00	[0.97, 1.04]	1.00	[0.92, 1.08]
Child First-born status (No)						
Yes	1.05*	[1.01, 1.09]	1.05*	[1.01, 1.09]	0.96	[0.91, 1.02]
* p < 0.05, ** p < 0.01, *** p < 0.001	N= 72323		N= 72323		N= 72115	
	M&Z R^2= 0.098		M&Z R^2= 0.102		M&Z R^2= 0.100	

associated with the lowest likelihood of any invalid doses (aOR = 0.35, 95% CI 0.33-0.37) to children in North Dakota who are associated with the highest likelihood of any invalid doses (aOR = 4.50, 95% CI 4.17-4.84) when compared to California. Children from two states (GA, and OR) are as likely as children from California to have any invalid doses. Fifteen (15) states are associated with statistically significant lower aORs compared to California (AK, FL, IA, KS, LA, MI, MT, NV, NJ, OK, RI, SD, TX, VA, and WV), while the remaining states and D.C. (N = 33) are associated with higher odds of any invalid doses. Full state-data is available in Appendix D of this chapter.

Time is also associated with differences in invalid doses for the full series but with varying results by model. A change in the number of invalid doses between 2013 and 2014, shown in Table 3, is also demonstrated in the regression results. Compared to 2012, children in the 2014-2016 NIS are associated with lower odds of having invalid doses due to age (for 2016 the aOR is 0.72, 95% CI 0.62-0.83). When evaluating the effect of year on invalid doses due to interval, the trend is not consistent. Children in the 2013 sample are associated with higher odds (aOR = 1.37, 95% CI 1.34-1.40) of having an invalid interval dose, but in 2016 are associated with statistically significantly lower odds a(OR = 0.54, 95% CI 0.52-0.57) when compared to children in 2012.

Provider types are associated with invalid doses in different ways. Statistically significant differences are seen in the regression results primarily in relation to invalid doses due to age. Those children with “All Hospital” (aOR = 1.21, 95% 1.04-1.42) or “All Private” (aOR = 1.20, 95% CI 1.04-1.40) providers are associated with higher odds of invalid doses due to age when compared to those children with “All Public” providers. Conversely, those with “All Military/Other” providers have lower odds (aOR = 0.57, 95% CI 0.46-0.71) of having invalid

doses due to age when compared to those with the public providers. Those with "mixed" provider types are associated with statistically significantly higher odds of invalid doses in all three models. In the invalid interval model, only "Mixed Providers" are statistically significant demonstrating an increase when compared to all public providers (aOR = 1.65, 95% CI 1.43-1.91). As a check on whether multiple providers were influencing the coefficients, I tested a dummy variable that categorized children with one or two identified providers, who all responded to the survey, to control for whether all providers responded, and the results were not different (data not shown).

Mobility of children who have moved to a state different from where they were born is also associated with statistically higher odds of having invalid doses than children who did not move. Although both types of invalid doses are associated with higher likelihood in children who have moved, the odds are higher for those invalid doses due to interval (aOR = 1.87, 95% CI 1.65-2.12) compared to those due to age (aOR = 1.25, 95% CI 1.15-1.37). Receipt of a birth dose of Hep B is also associated with invalid doses. For example, children who have at least one provider report that the child received a Hep B birth dose have higher odds of an invalid doses due to age (aOR = 1.22, 95% CI 1.13-1.30) but have statistically significantly lower odds of having invalid doses due to interval (aOR = 0.74, 95% CI 0.67-0.81) when compared to those who did not receive the birth dose.

Other child-level factors associated with invalid doses are child age group, race/ethnicity, and first-born status. Children in the 25-29 months and the 30-35 months categories of higher odds of invalid doses due to age and interval compared to children in the 19-24 months age group. This trend held across all three models. For invalid doses due to age, both 25-29 months and 30-35 months groups were associated with increased odds of invalid doses (aOR = 1.18,

95% CI 1.11-1.25; and aOR = 1.25, 95% CI 1.19-1.32 respectively) and for invalid intervals (aOR = 1.15, 95% CI 1.06-1.25; and aOR = 1.17, 95% CI 1.06-1.29). There was some variability in different child race/ethnicities regarding invalid doses. When compared to White children, Black children are associated with lower odds of invalid doses due to age (aOR = 0.90, 95% CI 0.83-0.97) while children of Multiple/Other race ethnicity have higher odds of invalid doses due to age (aOR = 1.12, 95% CI 1.03-1.21). Regarding invalid doses due to interval, Black, Hispanic, and Multiple/Other racial/ethnic groups demonstrate higher odds of invalid doses (aOR = 1.41, 95% CI 1.20-1.66; aOR = 1.25, 95% CI 1.10-1.43; and aOR = 1.58, 95% CI 1.39-1.79 respectively). Finally, children who are first-born in their families are more likely to have invalid doses due to age (aOR = 1.05, 95% CI 1.01-1.09) compared to those who have older siblings.

Maternal characteristics, including age group, income and poverty status, and some levels of education, are also significant predictors of invalid doses. The younger maternal age group is associated with higher odds of invalid doses due to interval only (aOR = 1.13, 95% CI 1.04-1.23). Maternal education is only associated with invalid doses due to age. Mothers with less than high school education, high school degree, and some college but no degree all have similar lower odds of invalid doses due to age when compared with mothers with college degrees (range aOR = 0.87-0.89, 95% CI range 0.79-0.95). Finally, mothers who are in the highest income category (Above poverty, > $75k) are associated with lower odds of invalid doses due to interval than all other categories. As income decreased, or as households fell below the poverty line, the association with invalid doses due to interval increased. Children in families above the poverty line, but income < $75k had an aOR = 1.19 (95% CI 1.08-1.32) while children below the poverty line had an aOR = 1.38 (95% CI 1.21-1.58). Children in families who did not provide their

income also had higher likelihood of invalid doses due to interval (aOR = 1.48, 95% CI 1.19-1.82).

Association between Hepatitis B vaccinations and invalid doses. In this section, I highlight differences between Hep B doses separate from those I present in Table 4.4 with state data in Appendix E. When including Hep B invalid doses (any, age, and interval) as the dependent variables, IIS participation is associated with statistically significant higher odds of having invalid doses when controlling for time, child, maternal, provider, and geographical characteristics. Shown in Table 4.5, the aORs for invalid Hep B doses due to age and interval in children whose providers participated in an IIS are 1.25 and 1.24 respectively (95% CIs 1.08, 1.44 and 1.11, 1.38) compared to children whose providers did not participate. Those children whose providers' IIS participation was unknown, also have higher odds of invalid Hep B doses (aOR 1.18, 95% CI 1.05, 1.34) compared to children whose providers did not participate in an IIS.

As demonstrated in Table 4.3, over time, children are associated with higher odds of invalid Hep B doses due to age with the highest odds occurring in 2015 (aOR 1.44, 95% CI 1.41, 1.47), though it is unclear if the decrease from 2015 to 2016 (aOR 1.18, 95% CI 1.14, 1.23) will continue. This trend is in the opposite direction of what is seen in the full models presented in Table 4.4.

There are few differences in provider type when compared to "All Public" providers. Children with "All Private" providers have lower odds of invalid Hep B doses due to interval (OR 0.80, 95% CI 0.69, 0.92). Conversely, children with "All Military/Other" providers are associated with significantly higher odds of having invalid Hep B doses due to age (OR 1.65, 95% CI 1.32, 2.15).

Table 4.5 Adjusted Odds Ratios of Provider IIS Participation on Invalid Hep B Dose Status

Logistic Reg. Models:	(1) Any Invalid		(2) Invalid Age		(3) Invalid Interval	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
IIS Participation						
None	Ref.		Ref.		Ref.	
Some/All Providers	1.24**	[1.08, 1.43]	1.25**	[1.08, 1.44]	1.24***	[1.11, 1.38]
Unknown	1.16*	[1.02, 1.31]	1.15	[1.00, 1.32]	1.18**	[1.05, 1.34]
Year						
2012	Ref.		Ref.		Ref.	
2013	0.87***	[0.85, 0.88]	0.83***	[0.81, 0.84]	0.75***	[0.72, 0.78]
2014	0.95***	[0.94, 0.97]	0.97***	[0.95, 0.98]	0.58***	[0.57, 0.59]
2015	1.46***	[1.43, 1.49]	1.44***	[1.41, 1.47]	0.99	[0.97. 1.01]
2016	1.16***	[1.12, 1.21]	1.18***	[1.14, 1.23]	0.55***	[0.53, 0.57]
Provider Type						
All Public	Ref.		Ref.		Ref.	
All Hospital	0.93	[0.81, 1.08]	0.97	[0.84, 1.11]	0.84	[0.70, 1.01]
All Private	0.86	[0.74, 1.00]	0.87	[0.76, 1.01]	0.80**	[0.69, 0.92]
All Military/Other	1.64***	[1.28, 2.11]	1.69***	[1.32, 2.15]	1.24	[0.99, 1.56]
Mixed	1.10	[0.99, 1.23]	1.11	[1.00, 1.23]	1.11	[0.97, 1.27]
Moved from birth state (No)						
Yes	1.16*	[1.01, 1.32]	1.12	[0.96, 1.29]	1.62***	[1.43, 1.83]
Hep B Birth Dose (None)						
≥ 1 Provider(s) reported	5.47***	[4.22, 7.08]	8.76***	[6.58, 11.67]	1.00	[0.88, 1.13]
Maternal Age						
≤ 29 years	0.99	[0.94, 1.04]	0.98	[0.93, 1.02]	1.07	[0.97, 1.17]
> 29 years	Ref.		Ref.		Ref.	
Maternal Education						
< 12 years	1.00	[0.89, 1.13]	0.94	[0.83, 1.07]	1.25**	[1.09, 1.43]
12 years (HS degree)	1.06	[0.98, 1.14]	1.03	[0.95, 1.11]	1.16*	[1.03, 1.31]
> 12 years, non-college grad	1.10**	[1.03, 1.16]	1.08*	[1.02, 1.15]	1.08	[0.98, 1.18]
College grad	Ref.		Ref.		Ref.	
Income/Poverty Status						
Above Poverty, > $75k	Ref.		Ref.		Ref.	
Above Poverty, ≤ $75k	1.07*	[1.01, 1.14]	1.07	[1.00, 1.14]	1.20**	[1.07. 1.34]
Below Poverty	1.03	[0.95, 1.11]	1.00	[0.93, 1.09]	1.34***	[1.20, 1.49]
Unknown	1.16*	[1.03, 1.32]	1.16*	[1.03, 1.32]	1.52**	[1.15, 2.01]
Child Age Group						
19-24 months	Ref.		Ref.		Ref.	
25-29 months	0.92**	[0.88, 0.97]	0.92**	[0.87, 0.96]	1.03	[0.91, 1.15]
30-35 months	0.82**	[0.77, 0.86]	0.81***	[0.77, 0.85]	0.98	[0.89, 1.08]
Child Race/Ethnicity						
White	Ref.		Ref.		Ref.	
Black	1.03	[0.95, 1.13]	1.00	[0.92, 1.09]	1.24**	[1.09, 1.42]
Hispanic	1.07	[0.99, 1.15]	1.06	[0.99, 1.14]	1.17**	[1.04, 1.31]
Multiple/Other	1.08	[0.98, 1.18]	1.05	[0.95, 1.16]	1.43***	[1.26, 1.62]
Child Gender (Male)						
Female	1.00	[0.97, 1.04]	1.00	[0.97, 1.04]	0.98	[0.93, 1.03]
Child First-born status (No)						
Yes	1.09***	[1.04, 1.13]	1.11	[1.06, 1.16]	0.95	[0.89, 1.02]
* p < 0.05, ** p < 0.01, *** p < 0.001	N= 73,193		N= 73,193		N= 73,001	
	M&Z R^2	0.097	M&Z R^2=	0.101	M&Z R^2=	0.103

Maternal characteristics appeared less associated with invalid doses overall except for a few notable differences. Children who have at least one provider reporting a birth dose of Hep B are associated with significantly higher odds of invalid doses due to age (OR 8.76, 95% CI 6.58, 11.67) compared to children with no reported birth dose. Maternal education and poverty indicators are not strongly associated with invalid doses. Lastly, older child's age groups are associated with lower odds of invalid Hep B doses due to age compared to the youngest age group. Children in the 24-29 months (aOR 0.92, 95% CI 0.87, 0.96) and 30-35 months (aOR 0.81, 95% CI 0.77, 0.85) age groups are associated with lower odds of invalid Hep B doses. Child race/ethnicity and first-born status are similarly associated with invalid Hep B doses as the full models discussed in Table 4.4.

Discussion

Immunizations are most effective when administered at the appropriate age and intervals between doses (Butte et al., 2001; Stokley et al., 2004). An increasingly complex vaccination schedule, increased utilization of multiple vaccination providers, and a lack of a unified national infrastructure for documenting and tracking immunizations are all obstacles to improving the accuracy and completeness of immunization histories, the timing and quality of vaccines, and increasing overall rates (Stokley et al., 2004; Stokley et al., 2001; Yusuf et al., 2002). This study focuses on inappropriate vaccinations through a retrospective evaluation of the validity of administered doses using strict interpretation of the ACIP's required ages and intervals between doses and includes the recommended four-day grace period for retrospective review. The literature on invalid doses is scarce and dated and little attention has been paid to link between invalid vaccinations and quality and the potential effects invalid vaccines have on overall immunity in the population. This study adds to the literature on invalid doses by providing an

updated analysis of invalid vaccines for the full series including 4 DTaP, 3 Pol, 1 MMR, 3 Hib, 3 HepB, 1 Var, and 4 PCV doses over a five-year period. It also examines the relationship between IISs and invalid doses using multiple logistic regression modeling and controlling for child, maternal, and geographical factors as well as type of immunization provider(s) and time to better understand how electronic information systems may relate to the quality of vaccinations.

Over the study period, 49 out of the 50 states, and the District of Columbia, utilized IISs in some capacity. Since IISs have the capability of forecasting needed vaccines in real-time, using algorithms incorporating the ACIP schedule, it is reasonable to assume that the improved systems for tracking and documentation of vaccines would lead to decreases in the numbers of invalid doses. Previously, invalid dose estimates ranged from 8% to 35.5% (Butte et al., 2001; Hamlin et al., 1996; Luman et al., 2002; Stokley et al., 2004), and in this study, which includes more vaccines and stricter adherence to ACIP guidelines for validity assessments, I estimate that about half of all children in the NIS had at least one invalid dose, mostly due to inappropriate Hepatitis B and Polio vaccination which is consistent with other literature (Butte et al., 2001). From 2012 to 2016, the rates of invalid doses declined slightly for DTaP and were relatively unchanged for MMR, Hib, PCV, and Var; and overall rates were consistent with previous literature using the 2002 NIS (Stokley et al., 2004). Frequency of invalid doses for Hepatitis B declined slightly from 2015 to 2016, but that was after a significant increase in rates from 2014 to 2015 and remains a large portion of overall invalid doses. Invalid doses for polio increase from 2015 to 2016 and is likely responsible for the overall invalid rate increase in the same time frame.

The increases in overall invalid doses in this study may be explained in several ways. First, in this study, I analyze more vaccines than what was included in previous studies. In 2000,

a new vaccine for PCV was licensed for children (The College of Physicians of Philadelphia, n.d.) and would not have been included in the full series in two studies (Butte et al., 2001; Luman et al., 2002) and in the other two studies, a select few vaccines were selected for analysis and did not include the full series (Hamlin et al., 1996; Stokley et al., 2004). Second, prior studies were not consistent in defining or differentiating invalid doses. For example, Luman et al. (2002) did not evaluate invalid intervals and Stokley et. al. (2004) did not differentiate invalid age from invalid intervals. A third explanation is that, for various reasons, providers are administering doses at inappropriate times and at increasing frequency. There were no schedule changes in the five-year study period that I could associate with the increases in invalid Hepatitis B and Polio doses, so the reasons for these increases are unclear at this time and justify further investigation.

The utilization of Immunization Information Systems (IISs) is one strategy widely recommended by public health officials to help improve the quality of doses delivered by recommending or forecasting needed vaccines in real-time and reducing vaccination record fragmentation which has the potential to improve the accuracy and completeness of records (Groom et al., 2015; National Vaccine Advisory Committee, 1999). Ideally, data from IISs would be utilized to examine the effect of IISs on vaccination rates but currently still suffer from quality concerns and data are frequently incomplete (Khare et al., 2006). Therefore, utilizing a well-validated survey, such as the NIS, to examine immunization data is more appropriate in this setting. From 2012 to 2016, more than 72% of the children in the sample had providers who reported immunization data to an IIS which allowed for this analysis.

Overall, I find no effect of IIS participation on invalid vaccine status, similar to a previous study (Davidson et al., 2003), when I excluded Hepatitis B doses as an outlier vaccine.

However, when examined separately, IIS participation was associated with higher likelihood of invalid Hepatitis B doses. This is an interesting finding since only two of the three doses in the series were assessed for validity due to age, and all three were utilized in the interval validity determination. There is no minimum age for the birth dose of Hepatitis B and those who had providers that reported these birth doses were associated with higher odds of invalid doses than children whose providers did not report one. Previous studies have discussed the complexity surrounding the Hepatitis B schedule, and the difficulty providers had in determining the patient's need for a HepB vaccine (Butte et al., 2001), however, those recommendations have not changed in recent years and may not explain the significant increase in invalid doses especially in light of IISs ability to forecast vaccines that are needed in real-time.

One factor that contributed to the frequency of invalid doses is the whether a child received the birth dose of Hep B, the only vaccine currently recommended at birth. Children with at least one provider reporting that a HepB birth dose was administered were far more likely to have received invalid doses than children whose providers did not report a birth dose, however, that may also be due to the fact that those children were less likely to receive the Hepatitis B sequence overall.

This study was unable to account for several potential factors that could influence IIS participation, demonstrated by how little variance the regression models explained. For example, provider characteristics are largely absent from the NIS. The type of practice of responding providers is available but only in aggregate at the child-level. Therefore, individual providers' behaviors are not able to be explored with this data set. Providers are instrumental in providing immunization data to the NIS and low response rates and a lack of publicly available information regarding provider practices hinders analysis at the provider level. In the 2016 NIS, only 54.2%

of children had adequate provider data so roughly half of children with completed household interviews were excluded from analysis because they lacked immunization data from their provider(s) (National Center for Immunization and Respiratory Diseases, 2017).

Second, parental behaviors are not captured in the NIS. I include the receipt of a HepB birth dose, socioeconomic variables which are linked with attitudes and acceptance of vaccines, and demographics (Luman et al., 2003) to proxy for parental immunization behaviors. Starting in 2012, the NIS ceased asking parents to recall childhood vaccinations in an attempt to increase response rates by shortening the screening interview (National Center for Immunization and Respiratory Diseases, 2017). However, this information provided insight to parental awareness of child vaccination status.

Finally, since IISs are implemented and governed at the state-level, there is an important relationship between states, year, and IIS participation, which are difficult to uncover with the data used in this study. I controlled for states fixed effects and year fixed effects, but other unobserved variables may have biased the findings of this study. In a study by Davidson et. al. (2003), the authors concluded that the "presence of a registry" was not sufficient to improve vaccination rates, but this was based on three years of data and only evaluated DTaP, Polio and Hib vaccines. Implementing a control for the length of time since IIS implementation may offer additional insight into the IISs' impact on UTD status1[1].

[1] I attempted to collect the IIS implementation year for each state IIS, and Washington, D.C., using a literature search, IIS website search, and contacts at AIRA, however data could not be obtained within the time frame for this dissertation.

Limitations

There are several limitations to this study. First, IIS participation was proxied for using a question in the provider record check phase of the NIS. However, in the public use dataset, the role of the person responding to the survey is not available. Further, for each child in the NIS, data from all providers who responded is aggregated in the public-use file so individual provider participation cannot be assessed. Since the information is self-reported, the data are subject to errors in understanding of the IIS participation at the practice and/or provider level.

Second, although rigorous criteria were used in determining validity of each dose in the NIS, it was not possible to determine valid "re-vaccinations". Therefore, some doses that were administered before the appropriate interval may have been valid if the interval was calculated based on different doses. I attempted to minimize the number of mis-classification errors by providing a conservative estimate, adding the four-days grace period suggested by the CDC, and using the required ages and intervals for each dose in a series rather than the minimum recommended cutoff values.

Third, I was only able to analyze those with adequate provider data (those with immunizations that were reported), and therefore cannot tell if those whose providers did not participate would have changed the outcome. Also, The NIS is not able a viable source of provider-behavior and is not meant to be analyzed at the provider-level. For the purposes of this analysis, it is possible that providers who chose not to participate in the provider record check phase of the NIS behave differently from those providers who did participate and may have introduced a source of bias into the results. Fourth, the sample size was relatively small for each state. I attempted to improve the sample size by pooling five years of data, however, my findings demonstrate wide confidence intervals.

Lastly, there are known limitations to the NIS as a source of immunization information. The NIS provides stable and reliable estimates at a national level but is not reliable at the state level. Decreasing response rates by households and providers also add challenges in obtaining reliable vaccine information, however, the NIS utilizes a complex stratified survey design and provides survey and provider weights that adjust for selection and non-response bias. In several cases, imprecise coefficients limited the interpretation of the findings.

Conclusion

Protection against vaccine-preventable diseases relies upon timely and accurate vaccination of the population. Vaccines that are delivered at sub-optimal timing can result in a less robust immune response. Invalid doses are important to the overall quality of vaccinations; counting all doses, including invalid ones, gives the appearance of being "vaccinated" but without the full protection of antibodies that are induced by vaccine exposure and leads to an under-protected community (Luman et al., 2002). Further, the spread of vaccine-preventable diseases in communities that believe they are protected can propagate vaccine hesitancy and a public perception that "vaccines are ineffective". Most invalid doses require re-vaccination which can also add significant costs and burden on the health care system (e.g. additional doctor's visits, vaccine supply costs). The findings in this study demonstrate a continued need for improving the quality of vaccination delivery in the U.S. and targeted efforts to reduce the numbers of invalid doses.

Immunization information systems are population-based electronic repositories with the capability of improving tracking, documentation, and forecasting of vaccination needs in real-time, but their impacts on the timeliness and quality of vaccine delivery are still emerging. Although these data suggest that IIS may not contribute to reductions in invalid doses, the NIS

may not be the optimal dataset to address the question of IIS effectiveness. Efforts to further improve the quality and completeness of IIS data will ultimately allow for more nuanced evaluation of the full impact of IISs on vaccination status at state and local levels. Continued research into the impact of IIS on immunizations will help public health officials, providers, and policymakers determine the amount of investments and strategies for improvement as the country continues to face increasing numbers of vaccine-preventable outbreaks.

Chapter 5 An Examination of Immunization Information Systems' Policies and State-level Vaccination Rates

Introduction

High levels of vaccination are needed to achieve adequate protection against vaccine preventable diseases (VPDs). In 2016, vaccination rates for the full combined series of routinely recommended childhood vaccines missed the Healthy People 2020 target of 80% in children 19-35 months of age (Hill et al., 2017; US Department of Health, Human Services, Office of Disease Prevention, & Health Promotion, 2012). Only 70.7% of children 19-35 months of age in the U.S. had received the recommended doses for the full combined series including 4 doses of Diphtheria Tetanus and acellular Pertussis (DTaP), 3 doses of Polio (Pol), 1 dose of Measles, Mumps, and Rubella (MMR), 3 or 4 doses of Haemophilus influenzae b (Hib) depending on the manufacturer, 3 doses of Hepatitis B (Hep B), 1 dose of Varicella (Var), and 4 doses of the pneumococcal vaccine (PCV), which was 1.5 percentage points lower than 2015 estimates (Hill et al., 2017). When examined separately, rates for Polio, MMR, and Hep B met the Healthy People 2020 individual vaccine targets of 90%; but lower rates were reported for DTaP, Hib, and PCV which was consistent with the decline for the combined series. Declining rates and missed vaccination targets represent a continued public health priority and presents an opportunity for improving immunization rates and overall protection against vaccine preventable disease.

Several factors contribute to these sub-optimal rates of vaccination. Among those factors is the lack of an efficient, coordinated way of tracking and documenting vaccinations in the U.S., an important challenge considering the vaccination schedule has become more complex in the number and timing of routinely recommended vaccines (Stokley et al., 2001). Documentation of vaccines in a patient's medical chart is mandatory but those records often exist only at the provider or clinic-level (Centers for Disease Control and Prevention, n.d.; Clark et al., 2006). Additionally, children are seeing multiple vaccine providers with increasing frequency creating

the opportunity for fragmented and incomplete records, record scattering across different health records systems, and increases the chances for missed vaccination opportunities (Stokley et al., 2001; Yusuf et al., 2002). Incomplete records also increase the likelihood that children will receive duplicate vaccines due to an inability to accurately assess individual vaccination status which can lead to over-immunization, increased costs due to the demand on vaccine supply, and increases in the number of provider visits needed to fully vaccinate a child (Linkins, 2001; Stokley et al., 2004). Incomplete records can also lead to inappropriate vaccination, or the administration of vaccines at the wrong age or spacing between doses, and oftentimes requires re-vaccination so that an optimal immune response and subsequent protection toward VPDs can be achieved (Butte et al., 2001; Stokley et al., 2004).

At the population-level, incomplete records present challenges when assessing the vaccination coverage at local, state, and national levels. Currently, the U.S. uses the National Immunization Survey (NIS), a nationally representative cross-sectional survey, to estimate the vaccination coverage in children 19-35 months old and in teens 13 to 17 years old (Centers for Disease Control and Prevention; Zell et al., 2000). However, the delay between data collection and release of survey results, as well as the small sample sizes in each state, makes estimating true vaccination rates challenging (Centers for disease control and Prevention; Hill et al., 2015; Salmon et al., 2006). Further, although the complex design of the NIS tries to minimize the selection and non-response bias (Zell et al., 2000), the data may still be subject to inadequate data resulting from record fragmentation, reporting errors, and incomplete records leaving a need for more robust data sources.

Immunization information systems (IISs) are confidential population-based electronic repositories that house immunization data and are one strategy recommended for reducing record

fragmentation and improving immunization rates in the U.S. (Stokley et al., 2001). They have shown promise in increasing immunization rates by preventing missed opportunities (Freeman & DeFriese, 2003), consolidating fragmented records (Kempe et al., 2001), decreasing immunization-related costs through reductions in over-vaccination (Feikema et al., 2000), or reducing re-vaccinations due to inappropriately delivered doses (Stokley et al., 2004). They also offer the capability of real-time data access (Muscoplat & Rajamani, 2017) which would reduce the delay between data collection and analysis.

Over the last three decades, numerous resources have been invested in IISs as a tool to increase vaccination coverage in the U.S. through expansion of their functionality and utility to standardize and coordinate vaccination documentation and tracking (Centers for Disease Control and Prevention, 2018b; Groom et al., 2015). IISs are operationalized primarily at the state-level and are therefore subject to wide variability in their design, implementation, operation, and utilization (Martin et al., 2015). As a result, a series of functional standards, as described below, were created to help immunization programs standardize their IISs and allow for some degree of interoperability or functioning across different electronic systems (Immunization Information Systems Support Branch within CDC/NCIRD, 2013). IISs should:

1. Support the delivery of clinical immunization services at the point of immunization.
2. Support the activities and requirements for publicly-purchased vaccine, including the Vaccines For Children (VFC) and state purchase programs.
3. Maintain data quality (accurate, complete, timely data) on all immunization and demographic information in the IIS.
4. Preserve the integrity, security, availability and privacy of all personally identifiable health and demographic data in the IIS.

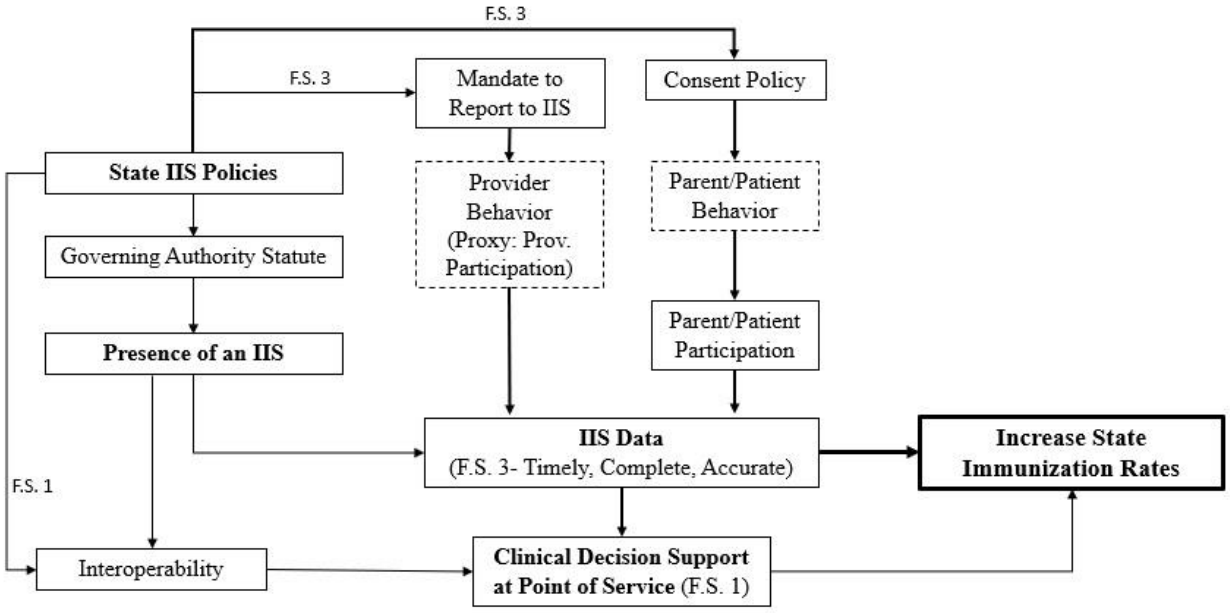
5. Provide immunization information to all authorized stakeholders.
6. Promote vaccine safety in public and private provider settings.

While the standards have provided structure for operationalizing IISs, and many IIS policies are created to align with these standards, evaluation of IISs are mostly limited to state-level analyses that may not be broadly applicable (Groom et al., 2015). Additionally, analysis of data from an IIS is still in early stages and data may not be reliable enough for accurate estimates. There are several studies in the literature regarding specific policies that govern the operation of IISs (Freeman & DeFriese, 2003; Hedden et al., 2012; Horlick et al., 2001; Martin et al., 2015) but the association of state-level policies immunization outcomes is not well-defined in the literature.

In this chapter, I analyze the relationship between policies as proxies for measuring the IIS functional standards and immunization rates at the state-level. To address this research aim, I examine two of the functional standards that guide the implementation and operation, supporting the delivery of immunizations at the point of service and data quality using several variables: the ability of states to forecast vaccine recommendations to electronic health records, the type of states' IIS reporting mandates, patient consent types, and IIS participation by providers. My working hypothesis is that states that have policies that meet the requirements of the functional standards, and those that encourage participation, will have a higher percentage of children who are up-to-date (UTD) for the full combined series of vaccines compared to states that do not meet the functional standards.

Conceptual Framework

In this chapter, I analyze the association between IISs and state immunization rates for the full combined series of routinely recommended vaccines which was guided by the conceptual framework in Figure 5.1.



F.S.= Functional Standard

Figure 5.1 Conceptual Framework for Increasing State Immunization Rates Using Immunization Information Systems

The Healthy People 2020 objectives describes several national programmatic immunization goals including an objective to vaccinate 80% of children with the full combined series by the age of two years (Healthy People 2020 [Internet], Office of Disease Prevention and Health Promotion). It is largely up to the individual states to govern their immunization programs and assess the progress and success of interventions designed to improve rates within the states (Hedden et al., 2012; Horlick et al., 2001). IIS policies influence state immunization rates by affecting IIS participation, utilization, or indirectly through operational mechanisms. In

this chapter, I focus on Functional Standards 1 and 3 since they are standards specifically related to the utilization of IISs and would theoretically have the largest impact on state immunization rates as I explain in the following paragraphs.

I examine the ability of IISs to provide clinical decision support at the point of care (described in Functional Standard 1). Interoperability, or the ability of an IIS to communicate with electronic health records (EHRs), is an important component of clinical decision support tools to assist providers with providing the right immunization at the right time (Dayton, 2014). One type of clinical decision support is the ability of an IIS to "forecast" or recommend vaccines using complex algorithms informed by the Advisory Committee for Immunization Practices (ACIP) immunization guidelines (Muscoplat & Rajamani, 2017). Theoretically, this would help ensure the patient is receiving the correct vaccination at the recommended age and appropriate interval between doses (Wood et al., 1999). Clinical decision support tools should also improve the completeness of the vaccination history since forecasts are available at the point of care when EHRs and IISs are interoperable (Muscoplat & Rajamani, 2017). This would reduce the chance for inappropriate or over-vaccination (Dayton, 2014) and should prevent missed vaccination opportunities while the patient is in the provider's office.

Participation in IISs is critical for the operation of an IIS. Providers who administer vaccines are the main source of IIS data and directly impacts the level of data accuracy, timeliness, and completeness in an IIS (described in Functional Standard 3) (Groom et al., 2015; Wood et al., 1999). Record fragmentation and incomplete records, which happens when there are multiple vaccine providers (Stokley et al., 2001), delays in reporting vaccines to an IIS (American Immunization Registry Association), and incomplete or inaccurate demographic information (Robison, 2015) are associated with lower immunization rates, inappropriately timed

doses, or extra doses of vaccines (Hamlin et al., 1996; Stokley et al., 2004; Wood et al., 1999). Providers' participation in IISs is driven by policies such as mandates that may require some or all providers/facilities to report immunizations to an IIS (Hendrickson et al., 2015; Horlick et al., 2001) as well as a provider's personal beliefs and behaviors toward immunizations and IISs (Gregorio et al., 1997; Kempe et al., 2017). It is difficult to capture provider behavior toward immunizing patients, so I proxy for this by including provider participation rates (Davidson et al., 2003) with the assumption that providers who provide fewer immunizations will not participate in IISs.

In combination with providers providing information to IISs, patient participation is also necessary. Patient participation occurs through a variety of mechanisms, and in this study, it will be proxied for using the type of IIS consent policy. IISs that use an explicit "opt-in" consent policy require patients/parents to give informed consent to have immunization data sent to an IIS. While this type of consent policy might place more power in the patient's hands with regard to medical data, it also leads to lower participation rates because it requires additional steps taken by the patients and providers to capture and document the consent (Boom et al., 2010). Implicit consent, or "opt-out" policies, assume that consent is provided unless patients choose to have their data opted out of the IIS (Horlick et al., 2001). This type of policy can lead to higher participation rates (Berry et al., 2013) but often parents are typically less aware of this exchange of personal data. Some states have strict mandatory consent policies that do not have an opt-out provision and in theory would have the highest patient participation rates.

While the literature surrounding the design and implementation of IISs is robust, there is a research gap in how well IISs are meeting the functional standards that guide them. This dissertation research explores this gap and adds to the literature on immunization information

systems by evaluating the association between IIS policies and state immunization rates as a measure of IIS success in meeting two of the functional standards.

Methods

Design. This study was a state-level retrospective analysis of IIS policies and the relationship with state-level immunization rates using secondary data from the 2016 Immunization Information Systems Annual Reports, 2015 IIS Legislative Survey, and the 2016 National Immunization Survey. I utilize descriptive statistics in combination with regression analysis to address the research aim guided by the Conceptual Framework in Figure 1.

Study sample. This study includes states (including Washington, D.C.) as the units of analysis (N = 51). New Hampshire was excluded because it did not operate an IIS during the study period, 2016, for a final N = 50. City-level IISs, Puerto Rico, and other territories were not considered for inclusion since information about how immunization programs and IISs were governed or operated was unclear, incomplete, or unavailable at the time of this study.

Data sources. This study incorporated data from three sources: the 2016 National Immunization Survey (NIS), the Survey of State Immunization Information System Legislation (IIS Leg) updated in 2015, and the 2016 Immunization Information System Annual Reports (IISARs). The data sources are described briefly below with specific variables and descriptions for inclusion presented in Table 1.

The IIS Leg and IISAR serve as the data sources for information on the IIS policies and progress toward meeting functional standards and achieving Healthy People 2020 immunization objectives (Centers for Disease Control and Prevention, 2018b). The IISAR is an annual report required by recipients of federal vaccine funding (Centers for Disease Control and Prevention,

2018b). Variables to proxy for the IIS functional standards, including clinical decision support, interoperability, and data completeness, were obtained from the IISARs for each state. The IIS Leg survey contains information specifically on IIS policies. Respondents are state immunization program personnel who are knowledgeable about the implementation and functionality of their state's IIS (Centers for Disease Control and Prevention, 2018b). IIS policies, such as governing authority, consent and reporting mandates, were used from this data set to proxy for participation in IIS. Information from both surveys are self-reported and respondents supplemented their responses with additional data sources such as census estimates (Centers for Disease Control & Prevention, 2015b).

Finally, state immunization rates were estimated from the NIS, the gold standard for immunization data in the United States (Khare et al., 2000). The NIS is a nationally representative population-based survey of households with children aged19-35 months and their immunization providers. Full details about the NIS methodology are available elsewhere in this dissertation. Immunization rates were estimated from the aggregated child-level immunization data collected from providers who participated in the record-check portion of the survey.

I merge the IIS Leg and IISAR datasets into a single data file matching on the Federal Information Processing Standards (FIPS) state codes. State-level immunization rates are first estimated in the NIS, as described in the Dependent variable section, and then coded directly into the merged data file.

Dependent variable. The dependent variable in this study is a state-level estimate for the percent of children 19-35 months old who are up-to-date (UTD) for the full combined series of vaccines defined as 4 doses of Diphtheria Tetanus and acellular Pertussis (DTaP), 3 doses of Polio (Pol), 1 dose of Measles, Mumps, and Rubella (MMR), 3 or 4 doses of *Haemophilus*

influenzae b (Hib) depending on the manufacturer, 3 doses of Hepatitis B (Hep B), 1 dose of Varicella (Var), and 4 doses of the pneumococcal vaccine (PCV). I select the full combined series, rather than another combination of one or more of the vaccines in the series, for two reasons. First, the overall rate of children up-to-date (UTD) for all routinely recommended childhood vaccines has consistently missed immunization programmatic targets (Healthy People 2020 [Internet], Office of Disease Prevention and Health Promotion) and, second, IISs help by reducing record fragmentation and missed opportunities (Freeman & DeFriese, 2003; Muscoplat & Rajamani, 2017); using an indicator for whether children received their full-series of vaccines reduces the need for determining whether there were missed opportunities because children who are UTD have received all necessary doses of vaccine.

The rates are estimated from the 2016 NIS using the recommendations from the 2016 ACIP child immunization schedule (Centers for Disease Control & Prevention, 2015a). Aggregated child-level immunization information was collected from providers who participated in the record-check portion of the NIS using provider weights included in the dataset. Children were included in the estimate if they resided in 49 states (excluding NH) and Washington, D.C., and if they had adequate provider data. Adequate provider data was defined in the NIS as having two or more doses reported by at least one provider (National Center for Immunization and Respiratory Diseases, 2017). During the data-verification stage, duplicate doses determined by date of administration were excluded (National Center for Immunization and Respiratory Diseases, 2017). The full combined series flag is a dichotomous variable within the NIS that is coded as a Yes/No the child received the full combined series. Based on the state of residence, I estimate the percentage of children in each state that have the full combined series flag. State

estimates are comparable to previous state rates from NIS-based rates from previous years (Hill et al., 2015).

I code the state-level rates as a continuous variable (0-100%) into the IIS Leg dataset in Excel using FIPS codes prior to merging the IIS Leg with the IISAR data.

Independent variables. For this study, I select variables to serve as proxies for measuring how well IISs are achieving IIS Functional Standards (See Table 1).

Table 5.1 Independent Variables Definitions and Descriptions

Measure	Variable	Data Source	Description	Measurement
IIS Participation	Mandate	IIS Leg	*Item:* Are any entities mandated (by legislation, regulations, rules or policy) to report immunizations to the IIS?	No Mandate, Partial Mandate, Full Mandate
Patient Participation	Consent	IIS Leg	*Item:* What type of consent is required from a parent before reporting immunization information for their child to your IIS?	Implicit, Explicit, Mandatory
Provider Participation	Private Non-VFC Provider Participation	IISAR	*Questions 40b & 41b:* Number of enrolled and reporting Private Non-VFC providers.)	Continuous (0-100%)-Calculated
Interoperability	Vaccine Forecasting Capability	IISAR	*Question 9:* In 2016, did your IIS send an immunization forecast to another system via HL7?	Yes/No

Participation. State mandate (Mandate), coded as "no mandate" if a state did not have a reporting mandate or reported that no entities are required to report; "partial mandate" includes those states that listed one or more entities (e.g. pharmacies, schools, public entities, private entities, VFC providers, schools) but not "all"; or "full mandate" if a state requires all immunization providers to report vaccines to an IIS. This data is captured in the IIS Leg Survey in response to the question, "Are any entities mandated (by legislation, regulations, rules or policy) to report immunizations to the IIS?". I include the mandate as one way to examine participation and the relationship between reporting laws on state immunization rates to measure

how well IISs maintain accurate, complete and timely data in an IIS as outlined in Functional Standard 3 (Horlick et al., 2001) because required reporting should theoretically improve the comprehensiveness of vaccination records.

Consent type is categorized as "Explicit" for those states requiring patients to opt-in, "Implicit" for those states requiring patients to "opt-out", and "Mandatory" for states that require participation. Consent policies determine whether patients, or parents/guardians, allow their immunization data to be sent to an IIS and directly affects the completeness of records within the IIS (Murthy et al., 2017); it can be thought of as less restrictive if patients have to manually provide explicit consent, or most restrictive if participation is mandatory. Of the 13 states with mandatory consent policies, only one state (MA) allows patients to opt out under specific circumstances and is included with the other mandatory consent states. This information is drawn from the IIS Leg survey in response to the question, "What type of consent is required from a parent before reporting immunization information for their child to your IIS?"

Provider participation is necessary for the success of an IIS (Freeman & DeFriese, 2003; Kim et al., 2007), particularly in the private sector (Linkins & Feikema, 1998) State participation rate for private non-Vaccines For Children (VFC) providers is included as a continuous variable (0-100%). The VFC program is a federally funded program and provides routinely recommended vaccines to uninsured/underinsured children, children on Medicaid, Alaskan Natives, and American Indians (Rein, Honeycutt, Rojas-Smith, & Hersey, 2006). Provider participation is collected in the IISARs as four different rates: public VFC providers, public non-VFC providers, private VFC providers, and private non-VFC providers (Centers for Disease Control & Prevention, 2015b).

Because many of the partial mandates require public and/or VFC providers to report data to an IIS (Centers for Disease Control & Prevention, 2015b; Horlick et al., 2001), I expect the public and VFC provider rates to be highly correlated both with each other and with the mandate variable. I select "Private non-VFC provider" rates because they are the providers least likely to be mandated to report immunizations to an IIS, as they are not participating in programs using federal funding for vaccines, and generally have lower participation rates compared to VFC providers (data not shown) (Freeman & DeFriese, 2003). Participation rates by these providers would provide a conservative estimate of the effect of provider participation on state immunization rates. I calculate the private non-VFC provider participation rate by dividing the number of actively participating providers by the number of enrolled providers in an IIS. One state (SC) did not report private provider rates so I impute a rate using mean substitution (Donders, Van Der Heijden, Stijnen, & Moons, 2006) in order to retain SC in the model. I test the model with and without SC to ensure that the imputed value would not introduce bias. I utilize the private non-VFC provider participation rate as a second proxy for data completeness because as provider participation increases, so should the overall number and completeness of the records in an IIS.

Interoperability. I include a binary variable for whether IISs actively send vaccine forecasts to providers' EHRs to proxy for the capability of an IIS to support the delivery of vaccinations at the point of care as described in Functional Standard 1. Improving immunization rates is partially dependent on accurately identifying the vaccines recommended for a specific patient, and then administering those doses at the right age and interval between doses (Dayton, 2014). At the state level, this can be accomplished by policies that guide the interoperability between IISs and provider EHRs (Dayton, 2014). Forecasting capability is collected by IISAR

respondents' answers to the question, "In 2016, did your IIS send an immunization forecast to another system via HL7?", a standard language for messaging between electronic systems (HL7 International, n.d.). An answer of "Yes" means that the IIS sent at least one vaccine forecast directly to a provider's electronic health record while "No" means it either did not have the capability or has the capability but is not currently being utilized by the IIS. An IIS's forecasting ability supports providers by enabling them to deliver vaccines at the point of care during an office visit and improves the quality of the vaccines by ensuring compliance with the vaccine schedule and helps prevent missed vaccination opportunities (Freeman & DeFriese, 2003).

Analysis. The analysis plan for this study includes summary statistics and multiple linear regression to address the research question. For summary statistics, I present frequencies in Table 5.2 for mandate type, consent type, ability to send vaccine forecasts, and display the range of rates for private non-VFC provider participation. I also present these data by state in Table 5.3.

I utilize two robust multiple linear regression models to examine the association between IIS policies for reporting mandate, consent type, interoperability, and the private non-VFC provider participation rates, and state-level UTD rates for the full combined series of childhood vaccines using two models shown below. In Model 1, I examine the direct effects between a reporting mandate, consent type, interoperability, and provider participation, and the state immunization rates for the full combined series. It is possible there is an interaction because policies and laws governing IISs often intersect with each other in complicated ways (Hedden et al., 2012). In Model 2, I examine the interaction between mandate and consent and report the predicted probabilities using the Stata margins command for this interaction in Figure 5.2. To

determine if predicted rates were different from each other, I examine the 95% confidence intervals for overlap.

In the regression model below, italicized variables are continuous and bolded variables represent those categorical variables with more than two categories for each state *i*:

Model 1: $state\_rate_i = \beta_0 + \beta_1 * \mathbf{Mandate_{i1}} + \beta_2 * \mathbf{Consent_{i2}} + \beta_3 * VaxForecast_{i3} + \beta_4 * \mathit{PrivNonVFCrate_{i4}} + \varepsilon_i$

Model 2: $state\_rate_i = \beta_0 + \beta_1 * \mathbf{Mandate_{i1}} + \beta_2 * \mathbf{Consent_{i2}} + \beta_3 * \mathbf{MandateXConsent_{i3}} + \beta_4 * VaxForecast_{i4} + \beta_5 * \mathit{PrivNonVFCrate_{i5}} + \varepsilon_i$

where β_0 is the estimated state up-to-date vaccination rate for the full combined series associated with no mandate and holding all other variables constant at zero; "Mandate" is the presence and type of mandate each state utilizes for reporting vaccinations to an IIS; "Consent" is the type of consent policy for each state for patient participation; "Mandate X Consent" is an interaction term between the mandate and consent variables and is included because of potential for one policy, such as a "full" or strict mandate requiring everyone to participate, increasing the likelihood of another strict policy such as consent type; "VaxForecast" is whether an IIS forecasts vaccine needs to provider EHRs; and "PrivNonVFCrate" is the percentages of private non-VFC providers who participate out of the number who enrolled in a state IIS. All analyses were performed with Stata version 15.1 (StataCorp, 2017).

Results

Summary statistics. The average state rate for receipt of the full combined vaccine series in children 19-35 months of age is 74.1% with the lowest rate (66.1%) in West Virginia and the highest rate (85.8%) in Maine.

Summary statistics for the predictor variables are shown in Table 5.2. Nineteen states reported no provider mandate to report vaccines to an IIS. Of the 31 states with a mandate, 18 (58.1%) had a full mandate requiring all immunization providers to report immunizations to an IIS and 13 (41.9%) required at least one, but not all, providers to report immunizations. Five (10%) of states required Explicit consent for patient's immunization data to be sent to an IIS while many states (N = 32) operated under an Implicit consent policy. Thirteen states (26%) have a consent policy mandating that child immunization data be reported to an IIS.

Table 5.2 Summary of Frequencies and Rates for IIS Policies and Provider Participation

Characteristic	Freq (N = 50)
Mandate	
None	19
Partial	13
Full	18
Consent	
Explicit	5
Implicit	32
Mandatory	13
Mandate X Consent	
None X Explicit	2
None X Implicit	15
None X Mandatory	2
Partial X Explicit	1
Partial X Implicit	11
Partial X Mandatory	1
Full X Explicit	2
Full X Implicit	6
Full X Mandatory	9
Vaccine Forecasting	
No	20
Yes	30
Private Non-VFC Provider Rate	Mean = 56.1%, Range (0 -100%)

In Table 5.3, IIS characteristics for mandate, consent, and interoperability, along with provider rates, are reported by state. When examined together, absence of a mandate and implicit consent occurred most frequently (N = 15) followed by partial mandate and implicit consent (N = 11) and full mandate with mandatory consent (N = 9). Two states, MO and NC, have no reporting mandate for providers but reported mandatory consent policy for patients'

participation. Partial mandates with Explicit and Mandatory consent policies are only reported in one state each, KS and OR respectively.

States are divided in their ability to forecast vaccines to provider electronic health systems; twenty states (40%) sent vaccine forecasts while thirty states (60%) did not demonstrate interoperability by sending vaccine forecasts to providers. Private non-VFC provider participation rate, calculated from the number of providers reporting two or more immunizations out of the total number enrolled, averages 56.1% across the states with the lowest reported rate (0%) in three states: CT, ME, and SD and the highest reported rate (100%) in RI.

Table 5.3 IIS Characteristics and Provider Participation by State

	AK	AL	AR	AZ	CA	CO	CT	D.C.	DE	FL	GA	HI	IA	ID	IL	IN	KS	KY	LA	MA	MD	ME	MI	MN	MO
Mandate																									
None	X	X			X	X						X			X			X				X		X	X
Partial										X			X	X		X	X		X		X				
Full			X	X			X	X	X		X									X			X		
Consent																									
Explicit											X						X								
Implicit	X	X	X	X	X	X	X			X		X	X	X	X	X		X	X		X	X	X	X	
Mandatory								X	X											X					X
Vac. Forecasting	X		X	X		X			X	X	X	X	X	X	X	X	X		X		X		X	X	
Priv. Non-VFC Rate	89.7	47.6	21.0	85.5	70.0	48.8	0.0	97.8	45.0	89.9	56.6	60.0	54.7	66.5	60.7	99.8	36.4	14.6	52.6	69.3	48.5	0.0	75.8	61.6	78.2

	MS	MT	NC	ND	NE	NJ	NM	NV	NY	OK	OH	OR	PA	RI	SC	SD	TN	TX	UT	VA	VT	WA	WI	WV	WY
Mandate																									
None		X	X		X						X		X			X			X			X	X		
Partial							X			X		X					X			X						X
Full	X			X		X		X	X					X	X			X			X			X	
Consent																									
Explicit		X									X							X							
Implicit					X	X	X	X		X			X			X	X		X	X		X	X		X
Mandatory	X		X	X					X			X		X	X						X			X	
Vac. Forecasting	X		X	X	X			X	X		X	X					X			X		X	X		X
Priv. Non-VFC Rate	41.5	32.5	81.9	50.3	43.3	31.7	36.8	67.3	55.4	62.6	48.5	89.9	33.0	100.0	56.1*	0.0	41.1	30.5	80.7	77.3	51.5	86.0	20.9	73.6	81.4

In Table 5.4, I present the results from the linear regression models to examine the direct effects from Model 1 between provider mandate to report immunizations to an IIS, a consent policy that would theoretically influence patient participation in an IIS, and private provider rates

as a proxy for providers' behaviors in IIS participation on states' UTD immunization rates and the interaction between mandate and consent types in Model 2

In Model 1, states with no reporting mandate UTD vaccination rates 4.0 percentage points higher than states with full reporting mandates (p = .012, 95% CI 0.94, 7.07) while there is no association for states with partial mandates. Consent type and vaccine forecasting did not have a statistically significant relationship with state UTD immunization rates. Private non-VFC

Table 5.4 Multiple Linear Regression Coefficients of IIS Policies and Provider Participation on State Up-to-Date Immunization Rates

Outcome: Est. State Rate Full Series	**Model 1 Coeff. (95% CI)**	***p***	**Model 2 Coeff. (95% CI)**	***p***
Mandate				
None	4.00 (0.94, 7.07)	.012	3.37 (-3.93, 10.67)	.360
Partial	3.05 (-0.51, 6.60)	.091	-4.92 (-8.10, -1.74)	.003
Full	*Ref.*		*Ref.*	
Consent				
Explicit	-4.18 (-10.30, 1.95)	.176	-3.81 (-13.11, 5.48)	.410
Implicit	-2.55 (-5.89, 0.80)	.132	-4.61 (-7.52, -1.70)	.003
Mandatory	*Ref.*		*Ref.*	
Mandate X Consent				
None X Explicit			-4.09 (-16.77, 8.60)	.520
None X Implicit			2.58 (-5.11, 10.27)	.500
Partial X Explicit			12.73 (2.96, 22.49)	.010
Partial X Implicit			9.41 (5.82, 13.01)	< .001
Forecast to EHR				
No	*Ref.*		*Ref.*	
Yes	-0.65 (-3.14, 1.84)	.600	-0.53 (-2.93, 1.88)	.660
Private Non-VFC Provider Participation	-0.07 (-0.13, -0.03)	.004	-0.07 (-0.12, -0.02)	.009
_constant	78.54 (75.38, 81.70)	< .001	78.81 (75.42, 82.19)	< .001
N= 50	**R^2 = .3096**		**R^2 = .4523**	

provider participation is negatively associated with states' UTD immunization rate. For every 10% increase in participation, states' UTD rates would be expected to decrease by 0.7 percentage points (p = .004, 95% CI -0.12, -0.02). The 56.1% mean private non-VFC provider rate (Table 5.3) means that in states with the average rate of participation, there would be a decrease of 4.9 percentage points on the UTD state rate compared to states where no private non-VFC providers

participated in an IIS. Private non-VFC providers do not participate in federally funded vaccine programs so their participation would be based largely on existing reporting mandates and their own behaviors, however, multi-collinearity between the mandate and non-VFC private provider rate was not demonstrable with this data.

In Model 2 (Table 5.4), the interaction between mandate and consent is statistically significant for partial mandate, but consent types did not vary in states with no mandate. Using marginal effects, the mean predicted state UTD rates for the interaction between IIS mandate and consent policies (shown in Figure 5.2) are all statistically significant with an R^2 = .4523.

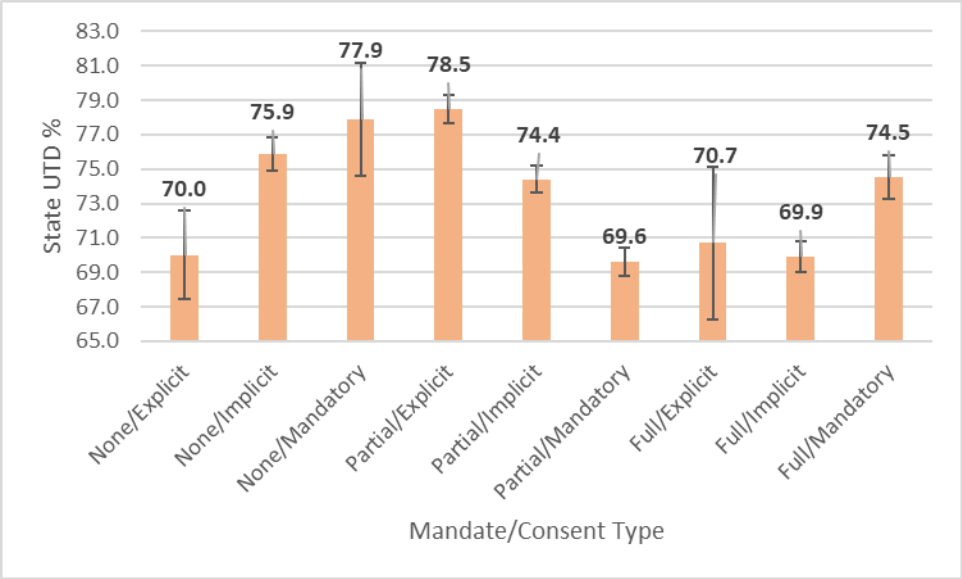


Figure 5.2 Predicted Up-to-Date Rates for the Interaction between Mandate Type and Consent Policies Using Margins

State UTD rates varied by consent types dependent on the type of reporting mandate that was present. Overall, based upon the confidence intervals, the highest predicted rates would be expected in states with no mandate and either implicit (95% CI 73.9, 77.9) or mandatory consent (95% CI 71.2, 84.6), partial mandate with either Explicit (95% CI 76.9, 80.2) or Implicit (95% CI 72.8, 76.0) consent, and states with a full mandate and Mandatory (95% CI 72.0, 77.0)

consent. The lowest predicted rates are expected in states with No mandate and Explicit (95% CI 64.8, 75.2) consent, Partial mandate with Mandatory (95% CI 68.0, 71.2) consent, or Full mandates with Explicit (95% CI 61.7, 80.0) or implicit (95% CI 68.1, 71.6) consent.

Within states that had no reporting mandate, rates generally increased as consent policies became more restrictive. Within states with no mandate, Explicit consent was predicted to have lower state UTD rates of 70.0% (95% CI 64.8, 75.2) than Implicit (75.9%) and Mandatory (77.9%) consent types which had overlapping confidence intervals (95% CI 73.9,77.9 and 71.2, 84.6 respectively). The opposite trend is predicted in states with partial mandates. In these states, the predicted UTD rates are highest in Explicit (78.5%, 95% CI 76.9, 80.2) consent states and lowest in Mandatory states (69.6%, 95% CI 68.0, 71.2). For states with full reporting mandates, there is no difference between Explicit and Implicit consent as their confidence intervals overlap (95% CI 61.7, 79.7 and 68.1, 71.6 respectively), but mandatory consent policies were associated with higher predicted UTD rates at 74.5% (95% CI 72.0, 77.0). Three of the mean predicted rates (None/Explicit, None/Mandatory, and Full/Explicit) have wide confidence intervals, likely due to the small number of states in those groups (Table 3), so I interpret these results with some caution.

Discussion

The U.S. consistently misses immunization targets published as part of the Healthy People Initiative. Utilization of IISs has been suggested as a strategy to improve vaccination rates by forecasting recommended vaccines in real-time for specific patients at the point of care and reducing record fragmentation by consolidating all immunizations in a confidential population-based centralized repository (Groom et al., 2015; Hedden et al., 2012; Stokley et al., 2001). Previously, literature has highlighted the challenges with variations in the design and

implementation of IISs at the state-level (Freeman & DeFriese, 2003; Hedden et al., 2012; Horlick et al., 2001) which ultimately led to the development of Functional Standards to guide the IIS implementation process (Groom et al., 2015). The complex dynamics between federal, state, and local policies governing IISs and immunization data further complicate the evaluation the success of these systems (Martin et al., 2015). Policies governing the current IISs have been described in detail elsewhere by Horlick et al. (2001), but the connection between states' policies and outcomes (immunization rates) are less clear and there is scant evaluative literature on how well IISs are meeting the functional standards.

This study contributes to the literature on IISs in three ways. First, I address a research gap in IIS evaluation research through an examination of policies governing the participation in IISs and state immunization rates. Individually, I find little association between mandate policies or consent types and UTD rates consistent with other literature on the effect of mandate types (literature on the effects of consent on immunization rates were not identified) (Kim et al., 2007; Mennito & Darden, 2010). However, I do find a statistically significant interaction between mandate policy and consent types that has not been previously reported in the literature. Trends for the predicted rates vary by consent type depending on mandate category and were uniquely different for each mandate type. In states with no reporting mandate, predicted rates increase as consent type becomes more restrictive (from explicit to mandatory), however, a decreasing predicted rate is associated in states with partial mandates- higher UTD rates in explicit consent states and lowest rates in states with mandatory consent. In states with a full mandate, there appeared to be no difference between implicit and explicit but mandatory consent was associated with higher UTD rates.

These findings add a new perspective to the available literature on IIS consent policies which has largely focused on how consent types relate to patient participation and costs associated with obtaining patient consent. Patient or parental consent is related to whether immunization data is included in an IIS (Hedden et al., 2012) and directly impacts the completeness of immunization records since non-participation can result in record fragmentation for those with multiple providers. Implicit and mandatory consent types are associated with higher participation (and inclusion of records) compared to explicit opt-in consent, though higher participation does not necessarily mean higher immunization rates as demonstrated in this study. In a randomized-controlled trial by Berry et. al, only 4% of parents opted out of an IIS compared to the explicit arm where only 21% of parents opted-in when extra steps were required for action (Berry et al., 2013). Boom et. al. explain that the effort, time, and cost required by health care officials and parents to opt-in are barriers to participation (Boom et al., 2010; Horlick et al., 2001). It is plausible that parents who voluntarily participate have different immunization behaviors than those who do not; the same can be hypothesized about parents who go through the effort to opt out of an implicit consent system though that rate is considerably lower.

Additionally, the studies by Kim et. al. (2007) and Mennito et. al. (2010) on the association between IIS mandates and immunization rates are more than ten years old. This means IISs have had the opportunity to mature and mandates more time to have effects on provider participation. However, the persistent finding of no association between mandate and immunization rates seems to suggest that there is more to the story than policy alone. Efforts should be made to improve data quality and providers' awareness about IISs and to have additional opportunities to comply with reporting mandates. My findings suggest that further

examination into the relationship between providers and parents may provide additional insight for improving rates and I discuss provider participation in the following paragraphs.

Participation in IISs is necessary by providers and patients to achieve complete, timely, and accurate immunization records in an IIS (Davidson et al., 2003; Kempe et al., 2001), a component of IIS Functional Standard 3. This study adds to the growing literature on provider participation in IISs. I found that increases in private non-VFC provider participation demonstrated a statistically significant negative association with state immunization rates for the full combined series of vaccines. Increasing provider participation rate would theoretically improve the quantity of data included in an IIS which should improve the completeness of records (Groom et al., 2015) in alignment with IIS Functional Standard 3, however, I found an inverse relationship.

Several factors could contribute to this unexpected finding. Provider behaviors toward vaccinations can impact immunization rates and may affect IIS participation it also influences parental immunization behaviors as they have been cited as the most important source of immunization information (Gellin, Maibach, & Marcuse, 2000; Taylor et al., 1997). While reporting mandates are meant to increase provider participation by requiring different entities to report vaccinations to an IIS, one study showed that, in spite of a mandate, many providers do not participate (Groom et al., 2015) suggesting a behavioral component to participation. Most states (67%) do not have enforcement procedures in place to ensure compliance with the mandate, though four states (AR, AZ, MI, and WV) do have penalties such as fines for not participating (Horlick et al., 2001). Additionally, some states may incentivize providers into enrolling in their IISs in order to increase participation rates in the IIS (U.S. Department of Health and Human Services, 2008). In states with penalties, overall provider participation was 79

to 86% (national mean = 68% across all provider types), except in WV which had a participation rate of 29% (data not shown), suggesting that mandates with penalties may not have universal effects.

As previously mentioned, IIS participation was not associated with UTD rates in this study except for lower odds when providers were unclear of their IIS participation, which may indicate a lack of knowledge about the availability and capabilities of IISs (Kempe et al., 2017). Previous research offers some support to this finding through reports of providers not utilizing IISs to their full potential (Clark et al., 2006), but specifics about how providers are utilizing IISs in practice remains a persistent gap in the literature and outside the scope of this dissertation (Groom et al., 2015). These findings suggest a possible association extending beyond policy and includes participant behavior, and the dynamics of provider-participant relationships.

This study also adds to the literature on IIS interoperability and immunization rates as a third contribution. I find that states' abilities to forecast immunization to provider EHRs through IISs is not associated with state UTD rates. Interoperability between IISs and electronic health records has been previously documented as an important step in improving the completeness and accuracy of patients' immunization histories (Groom et al., 2015). The IISs' ability to forecast vaccines to provider EHRs is used as a proxy for interoperability, theoretically improving immunization delivery at the point of care as laid out in Functional Standard 1. The literature suggests that forecasting vaccination needs to EHRs is important at the point of care to assist physicians with preventing missed opportunities and ensuring completion of the series on the age-appropriate schedule (Hinman et al., 2007). However, I identified only one study that tests the ability of IIS vaccine forecasting to improve rates (Bluml et al., 2017).

While Bluml et al. (2017) demonstrated improvements in the rate of adult influenza vaccines in a proactive study with pharmacists, I found no effect between the ability to forecast and UTD rates. Aside from methodological differences including a localized geographic region (Washington State), examination of a single vaccine rather than a complex series of routine vaccines, and differences in population, one possible explanation for the discordant results may be differences in IIS functionality. IISs are implemented in stages and because of variation in policies and resources, the systems mature at different rates (Linkins & Feikema, 1998). It is possible that Bluml and colleagues benefitted from utilizing a more mature IIS as compared with other states. Washington State's IIS was implemented in 1998 around the same time as large investments in IIS infrastructure occurred by the federal and states' government (Hinman et al., 2007).

Limitations

My study is affected by several limitations and I interpret my findings with caution as a result of these challenges. First, because this is a state-level analysis, my sample size of N= 50 increases the likelihood of type II errors and limits the statistical power. New Hampshire was excluded because it did not operate an IIS in 2016. South Carolina did not collect data on private providers in the IISARs, so I used mean substitution to impute the private provider non-VFC rate as described earlier. I tested the model with this rate and without SC included to test for an introduced bias and the results were similar.

Second, I am cautious about the findings for the mandate and consent variables on UTD state rates. In Model 1, states with "no mandate" were associated with statistically significantly higher UTD rates compared with states with full mandates, a finding that is counterintuitive to the conceptual framework and findings in other studies. One potential explanation is that there is

an omitted variable that has not been identified or for which data is not available at this time. Omitted variables are correlated both with the error term and the dependent variable which biases the coefficient on the independent variable. I tried to reduce this bias, without success, in the following ways: First, I considered whether states had expanded their Medicaid programs which would increase access to vaccines through the Vaccines For Children program and thus increase state immunization rates. Second, I considered whether the state was utilizing a "home-grown", or state-designed IIS, or if a known vendor with standardized infrastructure across multiple deployments was utilized which might impact the operation and functional capability of a state's IIS. Third, I examined whether immunization exemption policies or exemption rates were influencing state immunization rates and found no statistically significant effect. Fourth, I examined whether political ideology, which have known differences in approaching vaccine policies (Baumgaertner, Carlisle, & Justwan, 2018), were affecting state immunization rates and found no association in my model. Lastly, I examined the effects of using a dichotomous mandate variable for any mandate or none and while results were consistent with the literature and found no association between mandate and UTD rates, the dichotomous variable treats states with partial mandates (who may require as few as one entity type to report to an IIS) the same as states that requires all immunization entities to report to the IIS and I want to explore the relationships of different types of mandates.

Provider participation rates are self-reported by state immunization program staff on the annual IISAR and were subject to errors in reporting as states may not have an adequate way to estimate provider participation. Three states reported a private non-VFC participation rate of 0.0% (CT, ME, SD) which seems unlikely. I did not impute these values with the mean as these states provided a value unlike SC which left the question blank. Further, "participation" was

defined in the IISAR as the submission of two or more vaccines and I was unable to determine the extent of provider participation. It is possible that providers enrolled and sent minimal vaccines to the IIS, perhaps because of a reporting mandate, but do not routinely participate in IISs. It is also unclear if provider participation is ever re-evaluated for participation gaps once providers have sent immunizations.

Finally, both the IIS Leg and IISAR data are self-reported by immunization program staff and are subject to errors. The CDC offers support in completing these surveys and conducts follow-up interviews to verify any inconsistencies in reported data to identify and correct errors.

Conclusion

Immunization information systems are useful tools to consolidate fragmented records and improve overall immunization rates, however, the dynamic interactions between policy, providers, and patients add a layer of complexity to the evaluation of IISs. In this study, I evaluate the association between IIS reporting mandates, consent policies, interoperability and provider participation. I find that consent types have different relationships with states' UTD rates dependent upon the state mandate. Further, private non-VFC provider rates are negatively associated with UTD rates. Together, these suggest a unique relationship between policy, participation, and the provider-patient relationship that is worth further exploration. Finally, while interoperability is important for improving the communication between IISs and electronic health records, I find no association between sending vaccine forecasts to an EHR and UTD rates at the state-level. My findings are consistent with previous literature expands on the knowledge that exists about IISs and their potential for improving immunizations in the U.S.

Chapter 6 Conclusions

In the United States, immunization rates have consistently missed targets set forth by the Healthy People Initiative. Contributors to these sub-optimal rates are multi-faceted and include: 1) inefficient tracking and documentation of immunizations leading to incomplete or fragmented records and creates the potential for over-vaccination, 2) missed opportunities and the inability to determine vaccine needs at the point of care leading to under-immunized populations, and 3) the use of unapproved alternative vaccines schedules resulting from growing hesitancy among parents and providers. Coordinated investments into the design and implementation of immunization information systems (IISs) have led to widespread adoption of these electronic repositories to improve immunization rates. Previous research has demonstrated mixed results in the effectiveness of IISs to improve immunization rates.

The aim of this dissertation was to examine the relationship between immunization information systems and vaccinations for the full combined series of seven routinely recommended vaccines in U.S. children 19-35 months of age. Specifically, I conducted three related studies to examine the association between IIS policies and participation on child up-to-date status, invalid doses, and state-level UTD immunization rates. I focused on the utilization of IISs as well as policies as they relate to the functional standards that guide the operation of state IISs in the U.S. In two of the studies, I also controlled for provider type, and child and maternal factors that are known to affect immunizations. In studies 1 and 2, I use data from the National Immunization Survey and logistic regression modeling to examine the association between provider IIS participation and the probability of a child having the full combined series of vaccines and whether that participation was related to the probability of having invalid doses. In study 3, I use data from the IIS Legislative Survey, the IIS Annual Reports, and the National Immunization Survey and linear regression modeling to examine the relationship between state-

level provider reporting mandates, parental consent types, interoperability of IISs, and private provider participation on the state UTD rates.

Throughout this dissertation, I used study designs that were similar to previous literature, when examining UTD status and invalid doses, with a few key differences. First, studies rarely include state as a covariate or control variable to account for differences in state policies, programs, and economics, whereas I include state as an important predictor of immunization status. Second, previous literature includes the use of pooled NIS data to determine the effect of IIS participation on UTD status, however, previous studies frequently failed to control for the effect of time on the UTD outcome (Mennito & Darden, 2010; Racine & Joyce, 2007). In this study, I include the year as a control for changes in immunizations due to changes in time. Differences in my studies' models may contribute to differences in the child and maternal factors that differed from previous literature (e.g. child race/ethnicity) and that were associated with UTD status and invalid doses.

Summary of Findings

In Chapter 3, I evaluated the link between IIS participation and child UTD status. I found no association between IIS participation and child UTD status. Children whose providers were uncertain of their IIS participation, however, were associated with lower odds of child UTD. These findings are valuable as it demonstrates that even as IISs have had the opportunity to mature, the predicted relationship between IIS participation and improved immunization rates is still not able to be demonstrated.

In Chapter 4, the relationship between IIS participation and invalid immunizations was examined. First, I provided an updated analysis over a five-year period on the state of invalid doses and demonstrated that invalid doses are still problematic. Almost half of all children had at

least one invalid dose between 2012 and 2016. This is an important finding because current immunization estimates count all doses and doses that are administered too young, or too close together, may not stimulate a robust immune response. This leaves a child under-protected and may contribute to VPD outbreaks. Secondly, this study demonstrated a statistically significant relationship between IIS participation and invalid doses. Children whose providers participated in an IIS were associated with higher odds of invalid Hep B doses, although, no association was demonstrated with the remaining six vaccines in the full combined series. This finding is counter to my hypothesis and indicates that participation may not be reflective of utilization of IIS features.

Lastly, in Chapter 5, I analyzed the effect of an IIS provider mandate, patient consent policy type, vaccine forecasting feature, and private non-VFC provider participation rate and the relationship to states' UTD rates. I found no direct effect between mandate and consent on state UTD rates except for those states with no reporting mandate. In non-mandated states, UTD rates were 4.0 percentage points higher than states with full mandates. I also found a significant interaction between mandate and consent type. States with no mandate and mandatory consent demonstrated the highest mean predicted UTD rates. Taken together, these findings suggest that provider participation is important for success, but a mandate may not be the best way to compel participation. For patients/parents, mandatory consent for participation in an IIS offers the highest benefit.

Relationship between IIS participation and immunization rates and quality

Together, Chapters 3 and 4 examined the effect of IIS participation on child UTD status and the probability of having an invalid dose. I hypothesized that IIS participation would be associated with increased probabilities of child UTD status and lower probability of invalid

doses. Taken together, I fail to reject the null hypotheses for these two questions, however, there was value in the findings.

Similar to previous studies that examined IIS participation (Kim et al., 2007; Mennito & Darden, 2010), I found that IIS participation was not associated with the probability of a child being UTD for their full combined vaccine series. In Australia, following the implementation of an IIS and two years later an incentive program for participation, an increase in immunization rates of almost 30% was demonstrated (Groom et al., 2015). In 1995, the CDC launched a quality improvement program, AFIX, to help providers increase immunization rates and incentivized provider participation in IISs. Studies by Kim et. al. (2007), and Mennito and Darden (2010), were conducted nearly ten years after the start of AFIX, and this dissertation work more than 20 years after its implementation. Failure to reject the null of no association between IIS participation and child UTD status persists despite the predicted theory of association. Further, my finding that children whose providers were uncertain of their IIS participation status were associated with lower odds of child UTD supports the work done by Kim et. al. (2007). These findings indicate that other factors, aside from participation, led to increases in immunization rates in Australia and have yet to materialize in the U.S.

While there was no effect between IIS participation and child UTD status, there was a statistically significant and unique relationship between IIS participation and the odds of having invalid doses that was not previously reported in the literature. From 2012-2016, invalid doses were largely driven by Hep B doses which led to separate analyses for Hep B. For Hep B doses, children whose providers participated in an IIS were associated with higher odds of invalid doses compared to those whose providers did not use an IIS. This is the first finding demonstrating a statistically significant relationship between IIS participation and immunizations, so I am

cautious about the interpretation that IIS participation leads to higher rates of invalid doses due to the complex history behind Hep B invalid doses in the literature (Luman et al., 2002; Stokley et al., 2004). This finding indicates that there may be differences between participation and utilization of IISs.

States and residential mobility relative to immunizations

Most discussions on immunization rates occur nationally and state-level discussions. However, immunization programs, and IISs, are operationalized at the state-level or local levels and would be expected to have policies, programs, economic, and environmental factors that affect immunization rates. My research found significant variation across the states with respect to estimated immunization rates, invalid doses, and how policies and participation were associated with immunizations. I selected California as the reference state for studies 1 and 2 because it is a large, diverse state with a relatively high UTD immunization rate (79.9%). Taken together, 28 states were associated with increased UTD odds but were also associated with significantly higher odds of invalid doses compared to California.

This finding suggests that some states may focus on the delivery of vaccines without regard to the timing or appropriateness of doses as all doses are counted in estimates of coverage. Interestingly, 13 states with increased UTD odds were associated with lower odds of invalid doses suggesting that high rates and appropriateness of doses were considered. These findings suggest there could be public health priorities, policies, or programs that exist to help states achieve higher quality immunizations. The findings could also indicate a difference in IIS maturity or availability of features, or an increased provider awareness of IISs and their capabilities.

Residential mobility, residing in a state different from where a child was born, was also statistically significant for lower odds of child UTD and higher odds of invalid doses, consistent with the literature (Stokley et al., 2004; Stokley et al., 2001). These children were less likely to have adequate provider data; those without adequate data were excluded from the studies. This difference in adequate data likely reflects the problem of record scattering and fragmentation, or a difference in provider behaviors toward immunizations (Dayton, 2014; Gaudino et al., 2002; Stokley et al., 2001). Together, these findings contribute valuable insight into the role of states on immunizations.

Providers' IIS participation and behaviors toward immunizations

Provider participation is mandatory for IISs to be effective, however, my findings, in conjunction with the literature, demonstrate that provider participation is complex. Providers can be categorized in several ways: public vs. private, VFC provider vs non-VFC provider, pediatrician vs. general practitioner vs. other immunization provider, or any combination listed (Centers for Disease Control and Prevention, 2018a). Although public providers are associated with lower immunization rates (Luman et al., 2002), private providers generally have lower participation rates than public providers (Gaudino et al., 2002) and may explain the following findings. In Chapters 3 and 4, I found no association between IIS participation and child UTD status or invalid doses for the full series, which appears counter to the claim that provider participation is necessary for improving immunizations rates. To add further complexity, in Chapters 3 and 4, children with "All private" providers were associated with higher odds of child UTD status and higher odds of invalid doses. In Chapter 5, I found a negative association between private non-VFC provider participation and state UTD rates further supporting that idea.

Participation in the VFC program is not associated with improved immunization rates (Kim et al., 2007). Often, public providers participate in the VFC program since they frequently receive state and federal funds for either Medicaid and/or VFC eligible patients (Dayton, 2014; Wood et al., 1999). In this dissertation, I did not include VFC provider rates in Chapter 5 because of the potential for multi-collinearity with the provider mandate. Mandates often specific that VFC recipients must report immunizations. However, my inclusion of a private non-VFC provider group is the first to categorize providers using multiple factors. This adds valuable insight for health officials trying to determine which providers may benefit from interventions to increase awareness and IIS participation might be needed.

Lastly, provider participation may be influenced by individual provider beliefs (Dayton, 2014; Gaudino et al., 2002). This is supported by the findings in Chapter 5 that found the greatest effect on state UTD rates in states with no reporting mandate. It is possible that when states do not require participation, those that choose to participate are more engaged in immunizations than those that are required to report but do not have intrinsic desire to do so, supporting the claim in the literature that mandates result in lower rates (Madewell et al., 2017).

Limitations

There were limitations to this work. First, the primary source for immunization data in the U.S. is the National Immunization Survey. Although the NIS is nationally representative and utilizes complex stratification, the cross-sectional design prevents causal analyses. The CDC and NCIRD employ several strategies to compensate for selection and non-response bias, as well as several quality measures to reduce errors in data collection. However, the survey relies on parents to accurately identify all immunization providers for the provider record check portion of the survey. Additionally, the record check portion of the survey is subject to additional non-

response bias and reporting errors in the self-reported immunization data. Although survey and provider weights were utilized where possible, I noted several differences in the groups that had adequate provider data and were included in the study compared with those who did not have adequate data. The NIS variables are available as mostly categorical variables and provider data is aggregated at the child-level which limits the analytical abilities.

Policy Implications and Conclusion

This dissertation research adds to the growing literature on IIS evaluation by examining the relationships of IISs on vaccination status. First, this work supports previous work done on IIS participation on UTD status as well as adds new findings not previously reported on. Earlier work suggests no effect of IIS participation, but over time, I expected that effect to materialize in alignment with IIS proponents' claims and work in other countries. My study supports the previous authors' work of no effect of IIS participation on child UTD status after controlling for provider type, state of residence, maternal, and child factors. It also supports the finding that there is a persistent knowledge gap about IISs. Children with providers who were uncertain of their IIS participation were associated with lower UTD odds. This work contributes new insights into the role of IIS participation on immunization quality by finding that IIS participation was associated with the odds of a child having invalid doses. These findings were driven largely by residential mobility and invalid Hepatitis B doses.

Second, this dissertation contributes to the literature by expanding the knowledge of how IIS policies affect state-level UTD rates. Few studies have examined the impact of policies such as mandate and consent type on UTD status and none have examined the impact of vaccine forecasting on state UTD rates for the full combined series. While my findings support the literature of no effect of mandate type or consent policies, I did identify a statistically significant

interaction between mandate and consent that offers additional insight into how policies may interact with each other to affect immunization rates. As mandates influence provider participation, and consent influences patient participation, this interaction highlights the importance of the provider-patient dynamic.

The third contribution this dissertation makes is by adding information about immunization variations across the states. While the previous contribution focuses on the state IIS policies, there may be state-level effects that influence immunization rates and invalid doses beyond IIS policy alone. Taken together, the findings from the two studies on IIS participation and UTD status and invalid doses resulted in interesting findings. Compared to California, a state that has a diverse population, and higher immunization rates, only four states were associated with lower odds of child UTD and three states showed no effect. However, of the remaining 41 states and association of higher UTD status, 28 states were associated with higher odds of invalid doses. This finding is particularly interesting because it suggests that there may be other state-level factors that encourage increasing the numbers of vaccines rather than appropriate or quality vaccination. Thirteen states had higher child UTD odds but lower odds of invalid doses which suggests higher rates and higher quality of immunization.

Overall, this dissertation work demonstrates the wide variation among states and their IISs on immunizations in the U.S. Improvement efforts should continue to focus on improving the quality of immunizations by reducing invalid doses and increasing provider awareness and participation in IISs. Further, IIS policymakers should take into consideration the interactions between different policy statutes. The lack of a reporting mandate was associated with higher participation rates than full mandates, when examining the interaction with consent policies,

highlighting the influence of provider behavior on immunization rates and the provider-parent dynamic.

Future Directions

The studies in this dissertation contributed in several meaningful ways to the IIS literature and stimulated ideas for future research questions. First, the wide variation of the between the relationship of states and immunization status raises questions about the effects of IISs on individual vaccine rates and invalid doses. It is possible that IISs are more effective on doses that are delivered on a similar schedule (DTaP, Hib, and Polio for example) than trying to accommodate the full combined vaccine series. Second, when considering the child UTD status and invalid doses together, the results did not always align with the state UTD rates. A deeper investigation into different policy interactions by state IISs may also provide insight as to the different dynamics that contribute to higher state UTD rates. Lastly, this dissertation work sparked my interest in investigating the effects of provider beliefs and behaviors on participation in IISs. The highest mean predicted rates were in states with no provider mandate rather than states that have a full mandate, counter to my conceptual framework. Exploring the different attitudes and examining provider characteristics in more detail with respect to how they relate to immunization participation may shed light on why researcher fail to see an effect between IIS participation and UTD rates.

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Appendices

Appendix A: Supplemental Table 3.1 Summary Statistics States by Adequate Prov. Data

	Full Sample	With Adequate Provider Data	Without Adequate Provider Data	*p*
State				< .001
Alabama	1.5%	1.5%	1.5%	
Alaska	0.3%	0.3%	0.3%	
Arizona	2.2%	2.3%	2.1%	
Arkansas	1.0%	1.0%	0.9%	
California	12.7%	11.2%	14.5%	
Colorado	1.7%	1.7%	1.6%	
Connecticut	1.0%	1.1%	0.8%	
Delaware	0.3%	0.3%	0.3%	
D.C.	0.2%	0.2%	0.2%	
Florida	5.7%	5.4%	6.0%	
Georgia	3.3%	3.3%	3.2%	
Hawaii	0.5%	0.5%	0.4%	
Idaho	0.6%	0.6%	0.5%	
Illinois	3.9%	3.9%	3.8%	
Indiana	2.1%	2.2%	2.1%	
Iowa	1.0%	1.1%	0.8%	
Kansas	1.0%	1.1%	0.9%	
Kentucky	1.4%	1.5%	1.2%	
Louisiana	1.6%	1.6%	1.6%	
Maine	0.3%	0.4%	0.3%	
Maryland	1.8%	2.0%	1.7%	
Massachusetts	1.8%	1.7%	1.8%	
Michigan	2.8%	3.1%	2.5%	
Minnesota	1.8%	1.8%	1.7%	
Mississippi	0.9%	0.8%	1.1%	
Missouri	1.9%	2.0%	1.7%	
Montana	0.3%	0.3%	0.3%	
Nebraska	0.7%	0.8%	0.6%	
Nevada	0.9%	0.8%	1.0%	
New Hampshire	0.3%	0.3%	0.3%	
New Jersey	2.6%	2.4%	2.9%	
New Mexico	0.7%	0.8%	0.6%	
New York	5.8%	5.6%	6.1%	
North Carolina	3.1%	2.9%	3.3%	

State	Full Sample	With Adequate Provider Data	Without Adequate Provider Data	*p*
North Dakota	0.3%	0.3%	0.3%	
Ohio	3.5%	3.4%	3.6%	
Oklahoma	1.3%	1.3%	1.4%	
Oregon	1.2%	1.5%	0.8%	
Pennsylvania	3.6%	3.8%	3.3%	
Rhode Island	0.3%	0.3%	0.3%	
South Carolina	1.4%	1.4%	1.5%	
South Dakota	0.3%	0.4%	0.3%	
Tennessee	2.1%	2.4%	1.7%	
Texas	10.2%	9.9%	10.5%	
Utah	1.3%	1.4%	1.1%	
Vermont	0.2%	0.2%	0.1%	
Virginia	2.6%	2.6%	2.6%	
Washington	2.3%	2.5%	2.0%	
West Virginia	0.5%	0.6%	0.5%	
Wisconsin	1.7%	1.8%	1.5%	
Wyoming	0.2%	0.2%	0.2%	
N	**27,339**	**14,988**	**12,351**	

Appendix B: Supplemental Table 3.2 Summary Statistics States by IIS Participation

	IIS Participation			
	None	**Some/All**	**Unknown**	***p***
State				< .001
Alabama	0.1%	1.3%	0.1%	
Alaska	0.0%	0.3%	0.0%	
Arizona	0.1%	2.0%	0.2%	
Arkansas	0.0%	0.9%	0.1%	
California	1.9%	5.9%	3.5%	
Colorado	0.1%	1.4%	0.2%	
Connecticut	0.1%	0.7%	0.4%	
Delaware	0.0%	0.2%	0.0%	
D.C.	0.0%	0.2%	0.0%	
Florida	0.1%	4.9%	0.3%	
Georgia	0.0%	3.2%	0.2%	
Hawaii	0.1%	0.3%	0.1%	
Idaho	0.0%	0.6%	0.0%	
Illinois	0.7%	2.6%	0.8%	
Indiana	0.1%	2.0%	0.1%	
Iowa	0.1%	0.9%	0.1%	
Kansas	0.3%	0.7%	0.1%	
Kentucky	0.4%	0.8%	0.2%	
Louisiana	0.0%	1.5%	0.1%	
Maine	0.0%	0.3%	0.0%	
Maryland	0.5%	1.1%	0.4%	
Massachusetts	0.4%	0.9%	0.5%	
Michigan	0.0%	2.9%	0.2%	
Minnesota	0.1%	1.5%	0.3%	
Mississippi	0.1%	0.7%	0.1%	
Missouri	0.7%	0.9%	0.5%	
Montana	0.0%	0.3%	0.0%	
Nebraska	0.1%	0.5%	0.1%	
Nevada	0.0%	0.7%	0.0%	
New Hampshire	0.2%	0.1%	0.1%	
New Jersey	0.2%	2.0%	0.3%	
New Mexico	0.0%	0.7%	0.0%	
New York	0.1%	4.9%	0.6%	
North Carolina	0.2%	2.5%	0.2%	

	IIS Participation			
State	**None**	**Some/All**	**Unknown**	***p***
North Dakota	0.0%	0.3%	0.0%	
Ohio	0.3%	2.5%	0.5%	
Oklahoma	0.1%	1.0%	0.2%	
Oregon	0.0%	1.3%	0.1%	
Pennsylvania	0.7%	2.3%	0.8%	
Rhode Island	0.0%	0.3%	0.0%	
South Carolina	0.1%	1.1%	0.3%	
South Dakota	0.0%	0.3%	0.0%	
Tennessee	0.4%	1.7%	0.3%	
Texas	0.8%	7.8%	1.4%	
Utah	0.0%	1.3%	0.1%	
Vermont	0.0%	0.2%	0.0%	
Virginia	0.5%	1.8%	0.3%	
Washington	0.1%	2.1%	0.3%	
West Virginia	0.0%	0.5%	0.1%	
Wisconsin	0.0%	1.7%	0.1%	
Wyoming	0.0%	0.1%	0.0%	

N = 14,751

Appendix C: Supplemental Table 3.3 Regression Results State aORs

State	aOR	95% CI	State	aOR	95% CI
Alabama	1.97***	[1.85, 2.11]	Montana	1.00	[0.93, 1.08]
Alaska	1.14***	[1.08, 1.20]	Nebraska	1.85***	[1.77, 1.94]
Arizona	1.00	[0.96, 1.05]	Nevada	1.22***	[1.15, 1.28]
Arkansas	1.28***	[1.20, 1.36]	New Hampshire	2.00***	[1.87, 2.14]
California	Ref		New Jersey	1.09***	[1.04, 1.13]
Colorado	1.45***	[1.39, 1.51]	New Mexico	0.87***	[0.81, 0.93]
Connecticut	1.86***	[1.79, 1.92]	New York	1.00	[0.95, 1.06]
Delaware	1.67***	[1.58, 1.76]	North Carolina	1.93***	[1.84, 2.01]
D.C.	1.20***	[1.13, 1.26]	North Dakota	1.17***	[1.09, 1.26]
Florida	1.08**	[1.02, 1.14]	Ohio	1.32***	[1.26, 1.39]
Georgia	1.63***	[1.53, 1.73]	Oklahoma	1.03	[0.98, 1.08]
Hawaii	1.57***	[1.48, 1.67]	Oregon	0.65***	[0.62, 0.69]
Idaho	1.25***	[1.17, 1.33]	Pennsylvania	1.72***	[1.64, 1.80]
Illinois	1.14***	[1.10, 1.18]	Rhode Island	1.38***	[1.31, 1.45]
Indiana	1.08*	[1.01, 1.15]	South Carolina	1.27***	[1.21, 1.33]
Iowa	1.47***	[1.38, 1.56]	South Dakota	1.43***	[1.34, 1.53]
Kansas	1.40***	[1.33, 1.47]	Tennessee	1.14***	[1.09, 1.20]
Kentucky	1.65***	[1.56, 1.74]	Texas	1.05	[1.00, 1.10]
Louisiana	0.94	[0.88, 1.01]	Utah	1.39***	[1.31, 1.47]
Maine	1.20***	[1.11, 1.29]	Vermont	1.64***	[1.52, 1.78]
Maryland	1.55***	[1.49, 1.61]	Virginia	1.16***	[1.11, 1.21]
Massachusetts	2.12***	[2.04, 2.20]	Washington	1.49***	[1.43, 1.56]
Michigan	1.29***	[1.21, 1.36]	West Virginia	1.10*	[1.02, 1.19]
Minnesota	1.45***	[1.38, 1.54]	Wisconsin	1.75***	[1.68, 1.91]
Mississippi	1.31***	[1.22, 1.41]	Wyoming	0.87***	[0.84, 0.94]
Missouri	1.34***	[1.27, 1.41]			

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Appendix D: Supplemental Table 4.3 Regression Results (Excl. Hep B doses)- State aORs

Logistic Reg. Models:	(1) Any Invalid		(2) Invalid Age		(3) Invalid Interval	
State	**aOR**	**95% CI**	**aOR**	**95% CI**	**aOR**	**95% CI**
Alabama	1.79***	[1.71, 1.88]	1.82***	[1.74, 1.90]	0.80***	[0.74, 0.85]
Alaska	0.38***	[0.36, 0.39]	0.36***	[0.35, 0.38]	1.16***	[1.09, 1.24]
Arizona	1.14***	[1.08, 1.19]	1.13***	[1.08, 1.19]	0.97	[0.92, 1.02]
Arkansas	1.91***	[1.80, 2.03]	1.94***	[1.83, 2.06]	0.53***	[0.49, 0.57]
California	Ref		Ref		Ref	
Colorado	1.15***	[1.10, 1.20]	1.12***	[1.07, 1.17]	0.50***	[0.47, 0.53]
Connecticut	1.39***	[1.33, 1.46]	1.41***	[1.35, 1.48]	1.08**	[1.03, 1.13]
Delaware	2.40***	[2.25, 2.56]	2.44***	[2.29, 2.61]	1.73***	[1.62, 1.85]
District of Columbia	2.09***	[2.00, 2.17]	2.15***	[2.07, 2.24]	1.89***	[1.77, 2.02]
Florida	0.73***	[0.70, 0.76]	0.74***	[0.71, 0.77]	1.24***	[1.18, 1.31]
Georgia	0.95	[0.90, 1.01]	0.94*	[0.89, 1.00]	1.32***	[1.23, 1.43]
Hawaii	2.24***	[2.15, 2.33]	2.28***	[2.18, 2.38]	0.76***	[0.71, 0.81]
Idaho	1.11**	[1.04, 1.18]	1.10**	[1.03, 1.17]	1.09	[1.00, 1.18]
Illinois	1.99***	[1.94, 2.03]	2.03***	[1.99, 2.08]	1.50***	[1.44, 1.56]
Indiana	1.77***	[1.69, 1.86]	1.76***	[1.67, 1.85]	1.86***	[1.73, 2.00]
Iowa	0.93*	[0.88, 0.99]	0.93**	[0.87, 0.98]	0.70***	[0.65, 0.76]
Kansas	0.73***	[0.70, 0.75]	0.73***	[0.71, 0.76]	0.84***	[0.80, 0.89]
Kentucky	1.82***	[1.74, 1.91]	1.82***	[1.74, 1.90]	0.95	[0.88, 1.03]
Louisiana	0.80***	[0.76, 0.85]	0.81***	[0.77, 0.86]	0.88**	[0.81, 0.95]
Maine	2.87***	[2.67, 3.08]	2.85***	[2.65, 3.05]	1.18**	[1.07, 1.30]
Maryland	1.14***	[1.10, 1.18]	1.15***	[1.11, 1.20]	1.15***	[1.09, 1.21]
Massachusetts	3.19***	[3.10, 3.27]	3.28***	[3.19, 3.37]	1.17***	[1.11, 1.23]
Michigan	0.75***	[0.70, 0.80]	0.77***	[0.72, 0.82]	0.62***	[0.57, 0.67]
Minnesota	1.77***	[1.66, 1.89]	1.82***	[1.71, 1.94]	1.30***	[1.21, 1.40]
Mississippi	3.38***	[3.18, 3.58]	3.49***	[3.29, 3.69]	1.28***	[1.18, 1.40]
Missouri	1.16***	[1.13, 1.20]	1.20***	[1.16, 1.24]	1.13***	[1.06, 1.20]
Montana	0.74***	[0.69, 0.79]	0.73***	[0.68, 0.78]	2.53***	[2.32, 2.75]
Nebraska	3.19***	[3.07, 3.31]	3.28***	[3.15, 3.41]	1.02	[0.96, 1.08]
Nevada	0.54***	[0.51, 0.56]	0.51***	[0.49, 0.54]	1.12***	[1.07, 1.18]
New Hampshire	1.61***	[1.54, 1.68]	1.64***	[1.57, 1.72]	0.81***	[0.75, 0.89]
New Jersey	0.89***	[0.85, 0.93]	0.92***	[0.88, 0.96]	1.25***	[1.20, 1.31]
New Mexico	1.73***	[1.64, 1.83]	1.77***	[1.68, 1.87]	1.51***	[1.44, 1.58]
New York	1.51***	[1.43, 1.59]	1.54***	[1.46, 1.62]	0.96	[0.91, 1.01]
North Carolina	1.06*	[1.01, 1.12]	1.08**	[1.02, 1.14]	0.46***	[0.43, 0.48]
North Dakota	4.50***	[4.17, 4.84]	4.62***	[4.28, 4.67]	0.63***	[0.57, 0.69]
Ohio	1.17***	[1.13, 1.21]	1.20***	[1.16, 1.24]	0.68***	[0.64, 0.72]
Oklahoma	0.79***	[0.76, 0.83]	0.82***	[0.78, 0.86]	0.71***	[0.67, 0.75]
Oregon	1.04	[0.98, 1.10]	1.06	[1.00, 1.12]	1.07*	[1.00, 1.15]
Pennsylvania	1.86***	[1.78, 1.93]	1.90***	[1.82, 1.97]	0.79***	[0.74, 0.84]
Rhode Island	0.35***	[0.33, 0.37]	0.33***	[0.31, 0.35]	1.29***	[1.22, 1.37]
South Carolina	1.18***	[1.14, 1.22]	1.20***	[1.15, 1.24]	1.03	[0.98, 1.10]
South Dakota	0.91*	[0.85, 0.98]	0.90**	[0.84, 0.97]	0.73***	[0.67, 0.79]
Tennessee	1.19***	[1.15, 1.23]	1.16***	[1.13, 1.21]	1.23***	[1.15, 1.31]
Texas	0.91***	[0.88, 0.95]	0.90***	[0.87, 0.94]	1.36***	[1.31, 1.42]

Utah	1.49***	[1.41, 1.59]	1.53***	[1.45, 1.63]	0.59***	[0.55, 0.64]
Logistic Reg. Models:	**(1) Any Invalid**		**(2) Invalid Age**		**(3) Invalid Interval**	
State	**aOR**	**95% CI**	**aOR**	**95% CI**	**aOR**	**95% CI**
Vermont	2.07***	[1.94, 2.21]	2.13***	[2.00, 2.27]	1.66***	[1.52, 1.81]
Virginia	0.94***	[0.92, 0.97]	0.97*	[0.94, 1.00]	1.04	[0.98, 1.10]
Washington	1.11***	[1.06, 1.17]	1.15***	[1.10, 1.20]	0.81***	[0.76, 0.85]
West Virginia	0.80***	[0.75, 0.85]	0.80***	[0.76, 0.85]	1.04	[0.95, 1.14]
Wisconsin	1.38***	[1.29, 1.48]	1.42***	[1.32, 1.52]	0.33***	[0.30, 0.36]
Wyoming	1.78***	[1.68, 1.88]	1.77***	[1.67, 1.87]	1.08	[1.00, 1.17]
* p < 0.05, ** p < 0.01, *** p < 0.001	N = 72,323		N = 72,323		N = 71,115	
	M&Z R^2 = 0.097		M&Z R^2 = 0.101		M&Z R^2 = 0.103	

Appendix E: Supplemental Table 4.4 Regression Results (Hep B doses)- State aORs

Logistic Reg. Models:	**(1) Any Invalid**		**(2) Invalid Age**		**(3) Invalid Interval**	
State	**aOR**	**95% CI**	**aOR**	**95% CI**	**aOR**	**95% CI**
Alabama	0.36***	[0.34, 0.38]	0.32***	[0.30, 0.34]	0.51***	[0.47, 0.54]
Alaska	3.70***	[3.44, 3.97]	3.93***	[3.64, 4.25]	1.66***	[1.57, 1.77]
Arizona	0.71***	[0.67, 0.75]	0.70***	[0.66, 0.74]	0.87***	[0.83, 0.91]
Arkansas	0.39***	[0.36, 0.42]	0.33***	[0.30, 0.36]	0.71***	[0.67, 0.76]
California	Ref		Ref		Ref	
Colorado	0.67***	[0.64, 0.70]	0.63***	[0.60, 0.66]	0.54***	[0.51, 0.56]
Connecticut	0.50***	[0.47, 0.53]	0.49***	[0.46, 0.52]	0.49***	[0.47, 0.51]
Delaware	0.32***	[0.30, 0.34]	0.33***	[0.31, 0.36]	0.29***	[0.28, 0.31]
District of Columbia	0.21***	[0.20, 0.22]	0.20***	[0.19, 0.21]	0.35***	[0.33, 0.38]
Florida	0.42***	[0.40, 0.44]	0.45***	[0.43, 0.47]	0.20***	[0.19, 0.21]
Georgia	0.43***	[0.40, 0.46]	0.41***	[0.38, 0.43]	0.34***	[0.31, 0.36]
Hawaii	0.45***	[0.43, 0.48]	0.46***	[0.44, 0.49]	0.70***	[0.65, 0.70]
Idaho	0.49***	[0.46, 0.52]	0.49***	[0.45, 0.52]	0.73***	[0.69, 0.78]
Illinois	0.45***	[0.43, 0.47]	0.43***	[0.41, 0.44]	0.63***	[0.61, 0.65]
Indiana	0.54***	[0.51, 0.58]	0.57***	[0.54, 0.61]	0.40***	[0.38, 0.43]
Iowa	1.41***	[1.33, 1.50]	1.40***	[1.32, 1.49]	0.57***	[0.54, 0.61]
Kansas	0.89***	[0.85, 0.93]	0.88***	[0.84, 0.92]	0.48***	[0.46, 0.50]
Kentucky	0.76***	[0.72, 0.80]	0.74***	[0.71, 0.78]	0.91**	[0.86, 0.96]
Louisiana	0.40***	[0.37, 0.43]	0.39***	[0.37, 0.42]	0.45***	[0.42, 0.48]
Maine	0.10***	[0.09, 0.11]	0.09***	[0.08, 0.10]	0.35***	[0.32, 0.38]
Maryland	0.66***	[0.63, 0.69]	0.66***	[0.63, 0.69]	0.52***	[0.50, 0.54]
Massachusetts	0.23***	[0.22, 0.24]	0.21***	[0.20, 0.22]	0.44***	[0.43, 0.46]
Michigan	0.56***	[0.51, 0.60]	0.54***	[0.51, 0.59]	0.53***	[0.49, 0.56]
Minnesota	0.56***	[0.52, 0.60]	0.48***	[0.45, 0.51]	0.63***	[0.60, 0.67]
Mississippi	0.64***	[0.59, 0.70]	0.66***	[0.61, 0.71]	0.34***	[0.31, 0.37]
Missouri	0.57***	[0.54, 0.59]	0.52***	[0.50, 0.54]	0.51***	[0.48, 0.53]
Montana	3.72***	[3.46, 4.00]	3.78***	[3.51, 4.07]	1.96***	[1.84, 2.09]
Nebraska	0.21***	[0.20, 0.22]	0.20***	[0.19, 0.21]	0.24***	[0.23, 0.25]
Nevada	0.67***	[0.64, 0.71]	0.69***	[0.65, 0.73]	0.73***	[0.70, 0.76]
New Hampshire	0.38***	[0.35, 0.41]	0.38***	[0.35, 0.40]	0.49***	[0.46, 0.52]
New Jersey	0.57***	[0.55, 0.60]	0.54***	[0.51, 0.56]	0.87***	[0.83, 0.90]
New Mexico	0.48***	[0.45, 0.50]	0.43***	[0.41, 0.45]	0.65***	[0.62, 0.68]
New York	0.41***	[0.39, 0.43]	0.36***	[0.35, 0.38]	0.67***	[0.64, 0.71]
North Carolina	0.38***	[0.35, 0.40]	0.35***	[0.33, 0.37]	0.48***	[0.46, 0.51]
North Dakota	0.37***	[0.34, 0.40]	0.27***	[0.25, 0.30]	0.76***	[0.71, 0.81]
Ohio	0.57***	[0.55, 0.60]	0.47***	[0.45, 0.49]	1.14***	[1.09, 1.20]
Oklahoma	0.61***	[0.57, 0.64]	0.57***	[0.54, 0.60]	0.54***	[0.51, 0.57]
Oregon	0.91**	[0.86, 0.97]	0.80***	[0.75, 0.85]	1.14***	[1.08, 1.19]
Pennsylvania	0.38***	[0.36, 0.40]	0.37***	[0.35, 0.39]	0.47***	[0.45, 0.50]
Rhode Island	8.74***	[8.23, 9.29]	9.51***	[8.85, 10.21]	1.87***	[1.78, 1.96]
South Carolina	0.88***	[0.84, 0.92]	0.83***	[0.79, 0.86]	0.99	[0.94, 1.04]
South Dakota	0.53***	[0.49, 0.57]	0.48***	[0.44, 0.52]	0.59***	[0.56, 0.63]
Tennessee	0.97	[0.93, 1.01]	0.90***	[0.86, 0.93]	1.32***	[1.25, 1.40]
Texas	0.51***	[0.49, 0.54]	0.59***	[0.47, 0.51]	0.68***	[0.66, 0.71]
Utah	0.87***	[0.82, 0.93]	0.89***	[0.84, 0.95]	0.51***	[0.48, 0.55]

Logistic Reg. Models:	**(1) Any Invalid**		**(2) Invalid Age**		**(3) Invalid Interval**	
State	**aOR**	**95% CI**	**aOR**	**95% CI**	**aOR**	**95% CI**
Vermont	1.65***	[1.54, 1.78]	1.54***	[1.44, 1.66]	1.24***	[1.15, 1.33]
Virginia	0.40***	[0.38, 0.42]	0.42***	[0.40, 0.44]	0.39***	[0.38, 0.41]
Washington	0.31***	[0.29, 0.32]	0.28***	[0.26, 0.29]	0.69***	[0.66, 0.72]
West Virginia	0.39***	[0.37, 0.42]	0.38***	[0.35, 0.41]	0.40***	[0.37, 0.43]
Wisconsin	1.17***	[1.09, 1.26]	1.18***	[1.09, 1.27]	0.72***	[0.68, 0.77]
Wyoming	0.49	[0.46, 0.53]	0.47***	[0.44, 0.50]	0.73***	[0.69, 0.78]
* p < 0.05, ** p < 0.01, *** p < 0.001	N = 73,193		N = 73,193		N = 73,001	
	M&Z R^2 = .252		M&Z R^2 = .307		M&Z R^2 = .103	